UNIVERSITY OF CALIFORNIA,
IRVINE

The Silyl Enol Ether Prins Cyclization: Application to the Total Synthesis of Cyanolide A
Synthesis of Quinolizidine and Indolizidine Heterocycles Using Intramolecular Aza-Diels–Alder Reactions
and
DanceChemistry: A Visual Teaching Aid

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Gidget C. Tay

Dissertation Committee:
Professor Scott D. Rychnovsky, Chair
Professor Larry E. Overman
Professor Christopher D. Vanderwal

2015

DEDICATION

To

My Parents, Sholin Tay and Shuchen Huang
My Brother, Wayne Tay

And

My Fiancé, Joshua Hirner

TABLE OF CONTENTS

LIST OF EQUATIONS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF ABBREVIATIONS

(+)-MIB	3-Exo-morpholinoisoborneol
2,2-DMP	Dimethoxypropane
Å	Angstroms
Ac	Acetate
aq.	Aqueous
BAIB	[Bis(acetoxy)iodo]benzene
biphep	biphenylphosphine
Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
Bu	Butyl
Bz	Benzoate
CBS	Corey-Bakshi-Shibata
cod	1,5-Cyclooctadiene
DBMP	2,6-Di-*tert*-butly-4-methylpyridine
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMP	Dess-Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DMAP	4-Dimethylaminopyridine
DMPU	1,3-Dimethyl-tetrahydropyrimidinone
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
Et	Ethyl
G	gram
h	Hour(s)
HMPA	Hexamethylphosphoramide
HRESIMS	High-resolution electrospray ionization mass spectrometry
HPLC	High pressure liquid chromatography
Hz	Hertz
i	*iso*
IR	Infrared spectrometry
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
L	liter
LC	Lethal concentration
LDA	Lithium diisopropylamide
LiDBB	Lithium di-*tert*-butylbiphenyl
μ	micro

m	milli
M	Molar
Me	methyl
MEM	2-Methoxyethoxymethyl
Mes	Mesitylene
MHz	Megahertz
min	Minute(s)
MOM	Methoxymethyl
MNBA	2-Methyl-6-nitrobenzoic anhydride
MS	Molecular sieves
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methylmorpholine-*N*-oxide
NOE	Nuclear Overhauser Effect
PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	Pivolate
PMB	*p*-Methoxybenzyl ether
Pr	propyl
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
rt	Room Temperature
rxn	Reaction
SAR	Structure Activity Relationship
t	*tert*
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butydimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
THPO	Tetrahydropyranone
TLC	Thin-layer chromatography
TMEDA	Tetrahmethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl

ACKNOWLEDGMENTS

- I would like to express my deepest appreciation to Professor Scott D. Rychnovsky. You were rarely on my case about how much research I was (or wasn't) getting done in lab. You had an open door policy, and I knew I could come to you with any questions or concerns no matter how big or small. You were always supportive of me participating in activates that would help further my career as an instructor. You have been an amazing PI.
- Professors Larry E. Overman and Christopher D. Vanderwal for participating on both my doctoral committee and advancement committee. You have been such great instructors, and I've been so fortunate to interact and learn from you.
- Dr. Kimberly D. Edwards and Professor Sheron Wray for being so supportive of my DanceChemistry project. This project would have never gotten off the ground without your help and encouragement. Thank you both for making the project what it currently is.
- Drs. Kimberly D. Edwards, Renee Link, Susan King, and Professor Robert M. Corn for providing excellent teaching and lab development opportunities. I have learned so much from each and every one of you. You were the ones that helped me realize what I wanted to do when I "grew up."
- I have been extremely blessed to have such amazing lab mates. Drs. Matt Perry and Nick Sizemore were like lab big brothers to me; you teased me mercilessly but I always knew I could come to you for advice. Dr. Maureen Reilly for being my "M.O.M" partner when I was a clueless younger graduate student. Dr. Wynne Kandur for your advice and guidance on life issues. Dr. Shawn Miller for keeping every day in lab entertaining. Renzo Samame for putting up with me as a bay mates all five years. Dr. Michael Holzwarth was someone I could talk to about anything, I'm so glad you were in the same bay as me, you will forever be my favorite angry German post-doc. Jacob Deforest, banana bros for life, thanks for being my LMFTPSM. Alex Wagner, Ali-get, enough said. Justin Hilf for being my teaching buddy; I've always appreciated your honest input, even if sometimes I don't like it so much. Greg Suryn for helping me with the DanceChemistry project and being an overall super nice person. Sarah Block for being my crazy cat lady friend/lab girlfriend.
- Chloe Huang and Christina Owens for your curiosity, willingness to learn, and fresh perspective of bench work; you remind me how fun and exciting chemistry can be.

- The Vanderboys: Dr. Samuel Tartakoff, Dr. Joey Carlson, Gregg Schwarzwalder, Dmitriy Uchenik, Dr. Jon Lam, and Dr. Anne Szklarski (Vandergirl?) for the priceless discussions, advice, and good times.
- Dr. Yili Shi for your patience and willingness to help me as a bright-eyed bushy tailed first year graduate student. Your mentorship and guidance during my first year was greatly appreciated.
- Professor K. C. Nicolaou, Dr. Andrea Nold, and Professor David Sarlah for introducing me to the world of organic chemistry research. The time I spent in the Nicolaou laboratory was instrumental to my early scientific development.
- Professors Yitzhak Tor, Katja Lindenberg, and Dr. Haim Weisman for your patience with me as I struggled to learn as much as could from you. Thank you for being amazing instructors, I will forever be grateful for your mentorship and wisdom.
- Ms. Perlita Guzman for introducing me to the topic of chemistry in 8th grade. You never know when teaching students how to balance equations will lead them down the path of becoming a future chemist. Thank you for showing me this path.
- The Tay, Huang, Liang, and Hirner families for all your love and support. I know that, regardless of what is happening in my life, you will always be there for me in whatever capacity I need from you. Thank you.
- My parents, Sholin Tay and Shuchen Huang for supporting me even though you didn't always fully understand what I was doing with my life. I know that when push came to shove, I could always count on you to be there for me.
- My brother, Wayne Tay for your unconditional love and support. I always knew I could turn to you for advice on any problem big or small. Thank you for always being there for me.
- My sister-in-law/god sister, Gen Lodevico for understand how graduate school vacation days and weekends work and helping explaining that to the rest of the family.
- And finally, Dr. Joshua J. Hirner for absolutely everything. You have been my rock all throughout graduate school. You have been my sounding board, editor/proofreader, motivator, friend, confidant, and love of my life. I will forever be indebted to you for all the support you have provided through my graduate school experience. I don't think I would have survived these five years without you by my side. You are amazing.

CURRICULUM VITAE

Gidget C. Tay

EDUCATION

Doctor of Philosophy Candidate, Organic Chemistry September 2010–May 2015
University of California, Irvine (UCI)
Dissertation: "The Silyl Enol Ether Prins Cyclization: Application to the Total synthesis of Cyanolide A, Synthesis of Quinolizidine and Indolizidine Heterocycles Using Intramolecular Aza-Diels-Alder Reactions, DanceChemistry: A Visual Teaching Aid"
Advisor: Scott D. Rychnovsky

Bachelor of Science, Chemistry; Minor in Dance September 2006–June 2010
University of California, San Diego (UCSD)
Honor: Magna Cum Laude
Advisor: K. C. Nicolaou

RESEARCH EXPERIENCE

University of California, Irvine January 2011– May 2015
Advisor: Professor Scott D. Rychnovsky

- Synthesized the natural product cyanolide A and analogues for evaluation of molluscicidal activity in a collaboration with a marine biomedical laboratory
- Developed a methodology to synthesize highly substituted tetrahydropyranones (THPOs) via a silyl enol ether Prins cyclization
- Completed computational studies of the newly developed THPO cyclization
- Developed a method to synthesize indolizidine and quinolizidine via a intramolecular cyano-azadiene Diels–Alder reaction

University of California, San Diego April 2009–June 2010
Advisor: Professor K. C. Nicolaou

- Carried out a multi-gram, multistep synthesis of a key building block towards synthesizing natural products, lomaiviticins A and B

AWARDS AND HONORS

UCI Commencement Speaker	June 2015
UCI Smitrovich Prize for "Meritorious Performance in Graduate Chemistry Research and Service"	May 2015
UCI Outstanding Contributions to the Department	May 2015
UCI Most Promising Future Teacher in Organic Chemistry Award	May 2014
UCI Pedagogical Fellow	March 2014
Second Place in the Orange County GWIS Spring Conference (Oral Presentation Division)	April 2013
UCSD Harold Urey Award Recipient for "Most Outstanding Graduating Chemistry Major"	June 2010
UCSD Chemistry Department, "Departmental Honors"	June 2010
Semifinalist in the Frank and Sarah McKnight Prize for "Outstanding Research Achievement"	October 2009

GRANTS

UCI School of Physical Science Travel Grant — March 2014 and 2015
Undergraduate Research Opportunities Program: Multidisciplinary Design Project — November 2014
UCI Associated Graduate Students Travel Grant — March 2014
UCI Graduate Student Workstudy Award — October 2012
National Science and Mathematics Access to Retain Talent Grant — September 2008–June 2010
The Academic Competitiveness Grant — January 2007–June 2008

CLASSROOM TEACHING EXPERIENCE

University of California, Irvine, CA

Head Teaching Assistant – General Chemistry Laboratory — Fall 2013–Spring 2015
Advisor: Dr. Kimberly D. Edwards

- Adapted published work into a new two week laboratory experiment
- Implemented electronic laboratory notebooks and introduced new lab equipment
- Encouraged active learning via in class presentations and online forums
- Supervised 22 TAs (teaching assistants; Fall 2013), 7 TAs (Winter 2014), 26 TAs (Spring 2014), 30 TAs (Fall 2014), 11 TAs (Winter 2015), & 25 TAs (Spring 2015)

Lecturer – Organic Chemistry — Summer 2014

- Instructor of record for 160 students
- Incorporated new active learning techniques into curriculum

Lecturer – Organic Chemistry Laboratory — Summer 2014

- Instructor of record for 70 students
- Supervised four teaching assistants

Teaching Assistant – Organic Chemistry — Summer 2013
Advisor: Dr. Susan King

- Lead weekly discussion sections

Head Teaching Assistant – Quantitative Analytical Chemistry — Spring 2013
Advisor: Professor Rachel W. Martin

- Lead weekly discussion sections
- Wrote practice problems

Head Teaching Assistant – Honors General Chemistry — Winter 2012, Fall 2011
Advisor: Professor Filipp U. Furche and Professor Robert M. Corn

- Lead weekly discussion sections
- Assessed student learning by writing exam questions

Teaching Assistant – General and Organic Chemistry Laboratories — Summer 2011, 2012, & 2013, Spring 2011 & 2012, Winter 2011, Fall 2010
Advisor: Drs. Kimberly D. Edwards, Renée D. Link, and Susan King

- Delivered original in-laboratory lectures

OTHER TEACHING/MENTORING EXPERIENCE

Educational Dance Chemistry Lectures — January 2012– June 2015
(http://www.youtube.com/user/DanceChemistry)
Create and develop educational videos that explain chemistry concepts through dance, bringing together students and instructors from both the chemistry and

dance departments at UCI in a collaborative manner; project funded by the Dean of Physical Sciences at UCI

Undergraduate Research Mentor — January 2013–June 2015
Mentor undergraduate students, Yu Yi Huang and Christina Owens, in the laboratory setting; developed research projects and taught them laboratory skills

Multidisciplinary Design Program Mentor — December 2014– June 2015
Designed and proposed a campus wide multidisciplinary research project called DanceChemistry. Through this project, I mentor UC Irvine students from multiple disciplines to develop multidisciplinary skills and knowledge

TA Professional Development Program Facilitator — October 2014
Planned and presented a two-day series of interactive workshops to provide new chemistry TAs with skills to begin their instructional careers

Train Incoming Teaching Assistants — September 2012–September 2014
Train new chemistry teaching assistants on effective teaching strategies in general chemistry laboratories

ACC Irvine Mentor Program — September 2010 –June 2011
Mentored undergraduate student, Jessica Friedman, to develop a competitive resume for post baccalaureate studies

PUBLICATIONS

(4) Tay, G. C.; Sizemore, N.; Rychnovsky, S. D. "Synthesis of Quinolizidine and Indolizidine Heterocycles Using Intramolecular Aza-Diels–Alder Reactions." *manuscript in preparation*.
(3) Tay, G. C.; Edwards, K. D. "New Visual Teaching Aid: DanceChemistry," *J. Chem. Ed. submitted*.
(2) Tay, G. C.; Huang, C. Y.; Rychnovsky, S. D. "Silyl Enol Ether Prins Cyclization: Diastereoselective Formation of Substituted Tetrahydropyran-4-ones," *J. Org. Chem.* **2014**, *79*, 8733–8749.
(1) Tay, G. C.; Gesinski, M. R.; Rychnovsky, S. D. "Formation of Highly Substituted Tetrahydropyranones: Application to the Total Synthesis of Cyanolide A," *Org. Lett.* **2013**, *15*, 4563–4539.

PRESENTATIONS

(9) Tay, G. C.; Edwards, K. D. "A Visual Teaching Aid: DanceChemistry," Center for the Integration of Research, Teaching and Learning Forum, College Station, TX, April 2015 (Poster Presentation).
(8) Tay, G. C.; Edwards, K. D. "New Visual Teaching Aid: DanceChemistry," Associated Graduate Students Symposium, University of California, Irvine, Irvine, CA, March 2015 (Oral Presentation).
(7) Tay, G. C.; Edwards, K. D. "New Visual Teaching Aid: DanceChemistry," 248th ACS National Meeting, San Francisco, CA, August 2014 (Oral Presentation).
(6) Tay, G. C.; Huang, C. Y.; Rychnovsky, S. D. "Silyl Enol Ether Prins Cyclization: Diastereoselective Formation of Highly Substituted Tetrahydropyran-4-ones," ACS Division of Organic Chemistry Graduate Research Symposium, Irvine, CA, July 2014 (Poster Presentation).
(5) Tay, G. C.; Huang, Y. Y.; Rychnovsky, S. D. "New Approach for the Diastereoselective Formation of Highly Substituted Tetrahydropyranones," 247th ACS National Meeting, Dallas, TX, March 2014 (Oral Presentation).
(4) Tay, G. C.; Byrum, T.; Gesinski, M. R.; Gerwick, W. H.; Rychnovsky, S. D. "Total Synthesis of Cyanolide A and Analogues," Orange County GWIS Spring Conference, Chapman University, Orange, CA, April 2013 (Oral Presentation).

(3) Tay, G. C.; Pereira, A. R.; Gesinski, M. R.; Gerwick, W. H.; Rychnovsky, S. D. "Synthetic Studies Towards Cyanolide A and Analogues," 245th ACS National Meeting, New Orleans, LA, April 2013 (Poster Presentation).
(2) Tay, G. C.; Gesinski, M. R.; Rychnovsky, S. D. "Synthetic Studies Towards Cyanolide A and Analogues," Graduate Student and Post-Doctorial Colloquium, University of California, Irvine, Irvine, CA, April 2012 (Oral Presentation).
(1) Tay, G. C.; Sarlah, D.; Nold, A. L.; Nicolaou, K. C. "Synthetic Studies Towards Lomaiviticins A and B," American Chemical Society Student Affiliates Undergraduate Research Symposium, University of California, San Diego, La Jolla, CA, May 2010 (Poster Presentation).

PROFESSIONAL SERVICE/OUTREACH

Chemistry Outreach Program — September 2010– June 2015
Visit local K-12 schools to perform chemistry demonstrations and excite the younger generation about chemistry

Science Fair Judge — September 2012– June 2015
Provide guidance for preliminary project design during "Ask a Scientist Night" and judge the science fair for the Irvine Unified School District and the Orange County Science and Engineering Fair (6th through 12th grade)

Iota Sigma Pi Officer: Outreach Coordinator — June 2013– June 2015
Plan outreach events and trips for a chemistry national honor society, participated in NCW awarded "Outstanding NCW Event" from ACS

UC Irvine CIRTL Forum Team — April 2015
Attended and presented at a conference to prepare future STEM faculty for the rapidly changing landscape of higher education. The three-person team was there to represent UC Irvine and included two Associate Deans.

Student-Hosted Organic Chemistry Seminar Committee — June 2013–February 2014
Hosted student-voted special departmental seminar speaker (Professor Jonathan Ellman, Yale) and planned his two-day schedule to meet with numerous graduate students and professors

Safety Video – UCSD Chemistry Department — July 2009
(http://chem-courses.ucsd.edu/CoursePages/Uglabs/143A_Weizman/EHS/EHS.html)
Participated in creating safety videos under the direction of Dr. Haim Weizman (UCSD), these videos were made to educate the chemical researchers of all University of California campuses on safe laboratory procedures

PROFESSIONAL DEVELOPMENT

Advance Pedagogical Seminar — April 2014–March 2015
Learned how to creating an inclusive learning environment for a diverse population of students; learned and implemented evidence-based pedagogies

Science Communication Skills Seminar — January 2014–March 2014
Critiqued and practiced creating compelling metaphors to make abstract science concepts memorable for non-experts

ABSTRACT OF THE DISSERTATION

The Silyl Enol Ether Prins Cyclization: Application to the Total Synthesis of Cyanolide A
Synthesis of Quinolizidine and Indolizidine Heterocycles Using Intramolecular Aza-Diels–Alder Reactions
and
DanceChemistry: A Visual Teaching Aid

By

Gidget C. Tay

Doctor of Philosophy in Chemistry

University of California, Irvine, 2015

Professor Scott D. Rychnovsky, Chair

A modular synthesis of the reportedly potent molluscicide, cyanolide A, was developed to provide facile access to a series of cyanolide A analogues. The synthesis of strategic derivatives was initiated in order to determine the structural features of cyanolide A required for molluscicidal activity. Cyanolide A was synthesized in twelve steps with an overall 2% yield. After extensive SAR studies, it was found that cyanolide A was not responsible for the reported molluscicidal activity observed in the original studies.

A diastereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyran-4-ones was developed. The key step of this methodology, a silyl enol ether Prins cyclization, was promoted by a condensation reaction between a hydroxy silyl enol ether and an aldehyde to afford substituted tetrahydropyran-4-ones. The cyclization was tolerant of many functional groups, and the modular synthesis of the hydroxy silyl enol ether allowed for the formation of more than thirty new tetrahydropyran-4-ones with up to 97% yield and >95:5 dr. The cyclization step forms

new carbon–carbon and carbon–oxygen bonds, as well as a quaternary center with good diastereoselectivity. The method provides a versatile route for the synthesis of substituted tetrahydropyrans.

The scope and diastereoselectivity of an intramolecular aza-Diels–Alder reaction starting from a variety of 2-cyano-1-aza-1,3-butadienes was explored. The key reactions involved in synthesizing the Diels–Alder precursors are an imine condensation and a Strecker reaction and subsequent oxidation. The method provides a route for the synthesis of substituted quinolizidine and indolizidine heterocycles containing a cyanoenamine functional group.

A visual aid teaching tool, the DanceChemistry video series, has been developed to teach fundamental chemistry concepts through dance. These educational videos portray chemical interactions at the molecular level using dancers to represent chemical species. Students reported that the DanceChemistry videos helped them visualize chemistry ideas in a new and memorable way. Surveying the general laboratory course at the University of California, Irvine (n = 1266), 75% of the students said they wanted to use these videos to learn additional chemistry topics in the future. Data from pre- and post-surveys show an increase in students' average scores after watching a five minute DanceChemistry video. These instructional videos are disseminated broadly through a dedicated YouTube channel, DanceChemistry.

Chapter 1

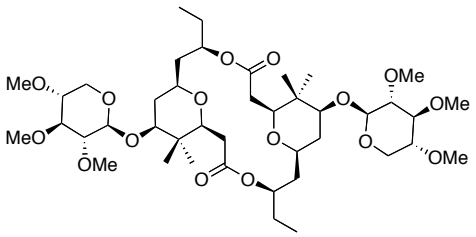
Total Synthesis of Cyanolide A

Abstract: A modular synthesis of the reportedly potent molluscicide, cyanolide A, was developed to provide facile access to a series of cyanolide A analogues. The key reactions involved are reductive alkylation, silyl enol ether Prins cyclization, and Shiina's lactonization. The synthesis of strategic derivatives was initiated in order to determine the structural features of cyanolide A required for molluscicidal activity. Cyanolide A was synthesized in twelve steps with an overall 2% yield. After extensive SAR studies, it was found that cyanolide A was not responsible for the reported molluscicidal activity observed in the original studies.

Structure and Isolation

In 2010, Gerwick and co-workers isolated the C_2-symmetric macrodiolide cyanolide A (Figure 1-1) from the extracts of cyanobacteria, *Lyngbya bouillonii*, collected near Pigeon Island, Papua New Guinea.[1] The structure of cyanolide A (**1-1**) was elucidated through extensive NMR analysis and HRESIMS, and determined to be a 20-membered dimeric glycosidic macrolide containing two tetrahydropyran rings and two xylose residues. The relative configuration and β-linkage of the two xylose residues was determined by examining coupling constants in the ^{1}H NMR and assuming that the xylose sugar was in its natural D-configuration.

Cyanolide A (**1-1**) was reported to have molluscicidal activity against *Biomphalaria glabrata* (LC_{50} = 1.2 μM) while maintaining only moderate toxicity to other aquatic organisms (such as brine shrimp; LC_{50} = 10.8 μM).[1] It also exhibits low cytotoxicity against H-460 human lung adenocarcinoma and Neuro-2a mouse neuroblastoma cell lines.[1] The discovery of cyanolide A, an environmentally benign and possibly cost-efficient molluscicide, provides a potentially promising solution for schistosomiasis, an endemic parasitic infection, by treatment of infested water sources.



cyanolide A (**1-1**)

Figure 1-1. Structure of cyanolide A (**1-1**)

Schistosomiasis: An Overview

Schistosomiasis, commonly known as bilharzias or snail fever, is the second most socioeconomically devastating parasitic disease in the world.[2] Almost 240 million people in developing countries are infected continuously or intermittently by schistosomiasis, and greater than 700 million people are at risk of infection.[3] It is the most deadly neglected tropical disease, killing an estimated 280,000 people every year. The disease is contracted when the freshwater *Schistosoma* flatworms penetrate the skin of people who come into contact with contaminated water. Common domestic chores such as herding livestock and washing clothing can put people at risk of contracting schistosomiasis. *Schistosoma* eggs can migrate into various tissues, where they may cause disease symptoms such as hepatomegaly, splenomegaly, bladder cancer, or kidney malfunction.[4]

The flatworm requires alternate development between snail hosts (belonging to the genus *Biomphalaria*) and mammalian hosts; both are necessary for maintaining the parasite life cycle (Figure 1-2).[4] The eggs enter the water via feces or urine (Figure 1-2, 1) and hatch to release motile miracidia (2). The miracidia find snail hosts (3) and develop to release cercariae (5). The infective cercariae are then transmitted to the human host through the skin while in contact with infected water sources. Paired adult worms migrate to the rectum of the human host; the female can produced anywhere from 300 to 3000 eggs, which are released back into the environment in the form of feces or urine (10).

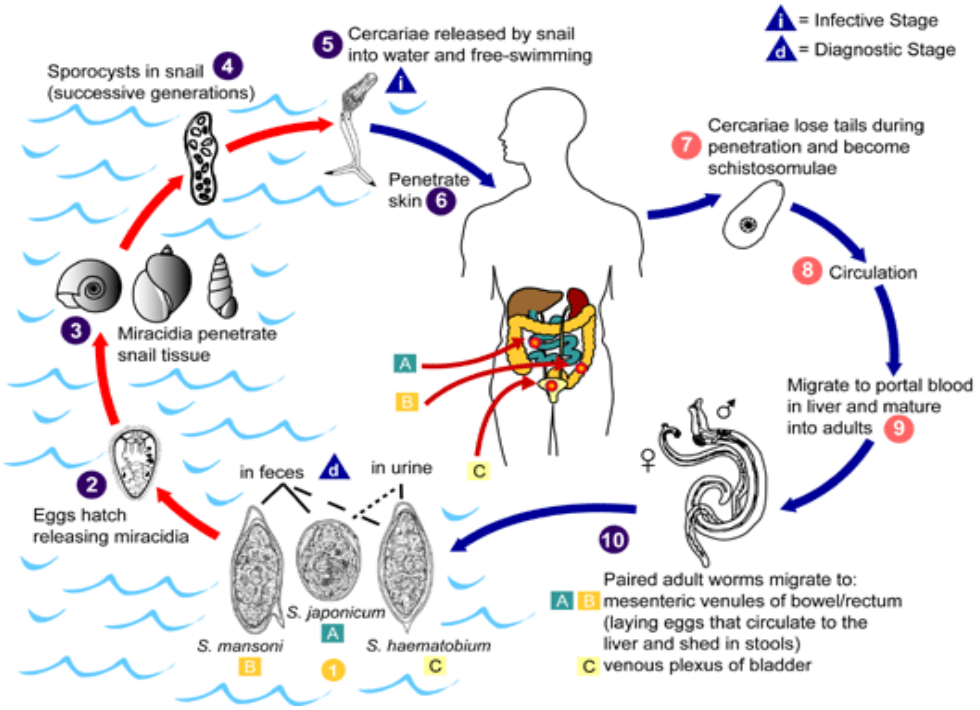


Figure 1-2. Infective cycle of schistosomiasis[6]

Eradicating the parasite from mammalian hosts with an anthelmintic drug such as praziquantel (Figure 1-3) does not prevent reinfection when in contact with a contaminated water source.[5] Therefore, reducing the population of the snail vector is a highly effective alternative method of schistosomiasis control because it curtails the susceptibility of reinfection. Niclosamide (Figure 1-3) is currently the only molluscicide recommended by the World Health Organization, even though it is expensive, prohibitively environmentally toxic, and has low water solubility.[4,7] With the need for other molluscicides, the discovery of environmentally benign cyanolide A (**1-1**) and its reported biological activity made it a very attractive target for many total synthesis laboratories, including the Rychnovsky group.

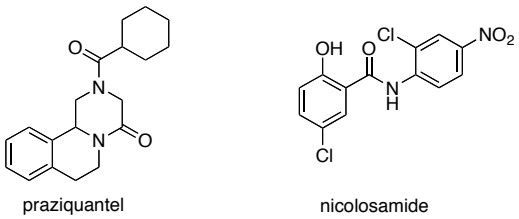


Figure 1-3. Current molecules used for the treatment or prevention of schistosomiasis

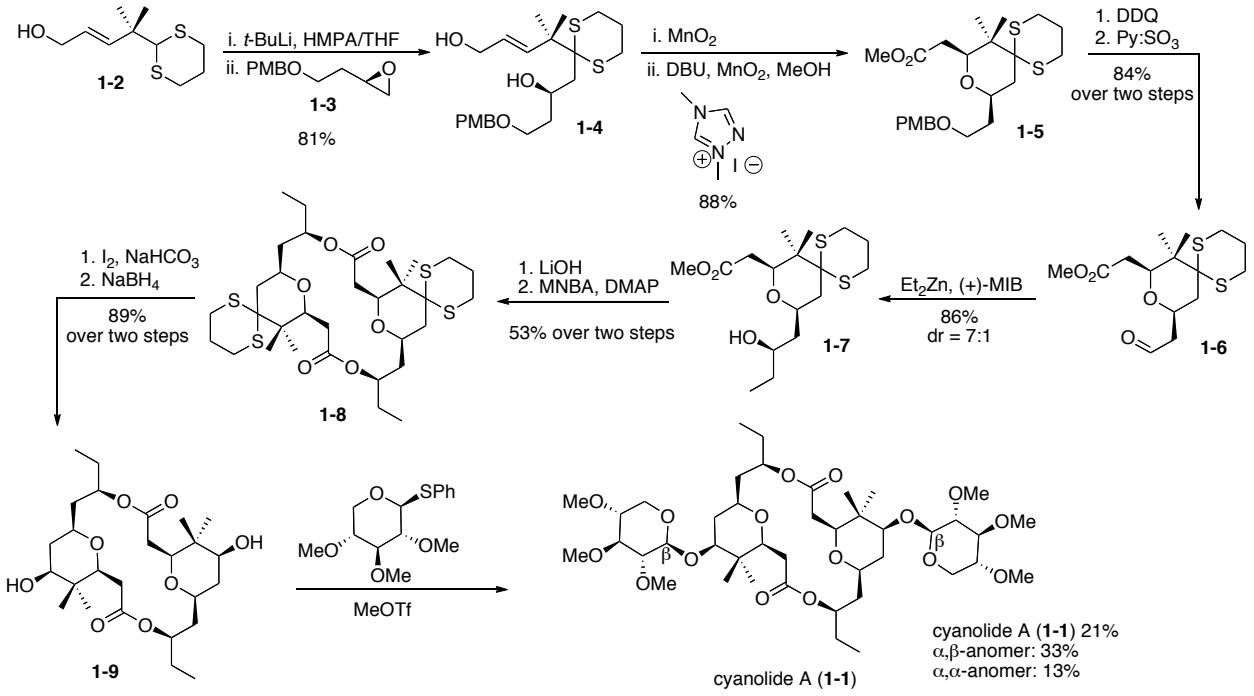
Other Syntheses

There have been multiple reported syntheses of cyanolide A and its aglycon. To date, there have been eight reports regarding the synthesis of cyanolide A. Most of the routes rely on a late stage esterification to form the macrodiolide core of cyanolide A (**1-1**). In every route, the incorporation of the two xylose moieties on the aglycon resulted in a mixture of diastereomers.

Hong's Syntheses

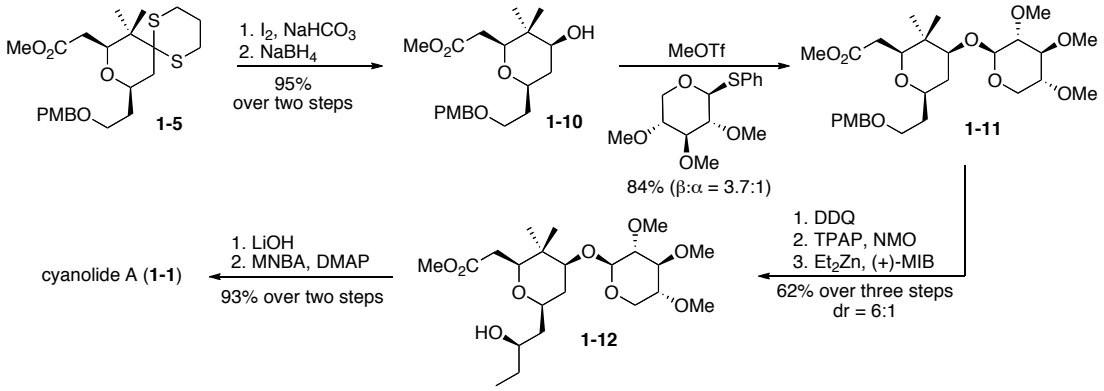
In May 2010, Hong and Kim reported the first total synthesis of cyanolide A starting from known 1,3-dithiane **1-2** and chiral epoxide **1-3** (Scheme 1-1).[8] A one-pot allylic oxidation, oxa-Michael, oxidation of **1-4** resulted in tetrahydropyran (THP) **1-5** as a single diastereomer. Removal of the PMB group followed by oxidation of the primary alcohol afforded aldehyde **1-6** in 84% over two steps. Asymmetric installation of the ethyl group using Et_2Zn and 3-*exo*-morpholinoisoborneol (MIB) as a catalyst resulted in alcohol **1-7** as a mixture of diastereomers. Hydrolysis of **1-7** followed by Shiina's lactonization[9] provided macrolide **1-8**. Deprotection of the 1,3-dithiane groups followed by $NaBH_4$ reduction of the resulting ketone completed the synthesis of cyanolide A aglycon **1-9**. Glycosylation of **1-9** afforded cyanolide A (**1-1**) along with the α,β-anomeric and α,α-anomeric isomers. The spectral data of synthetic cyanolide A (**1-1**) matched the natural sample completely; the optical rotation of the synthetic cyanolide A confirmed the absolute stereochemistry of cyanolide A reported by the Gerwick group.

Scheme 1-1. Hong's first-generation synthesis of cyanolide A **(1-1)**



The last glycosylation step resulted in 21% of the desired product and 46% of other isomers. In order to increase the efficiency of the route, Hong and Kim simultaneously reported an alternative, more efficient, synthesis of cyanolide A (Scheme 1-2). The second-generation synthesis featured glycosylation of the monomeric unit before dimerization. Intermediate **1-5** was deprotected and reduced to yield alcohol **1-10**. Glycosylation of **1-10** afforded a mixture of the desired β-anomeric monomer (66%) and undesired α-anomeric monomer (18%). Deprotection of the PMB group, TPAP-oxidation, and asymmetric ethyl addition resulted in **1-12** in a 6:1 diasteromeric ratio. Hydrolysis of ester **1-12** and subsequential dimerization resulted in cyanolide A (**1-1**). With the second-generation synthesis, cyanolide A was made in 10 linear steps starting from readily available compounds **1-2** and **1-3** in a 22% overall yield.

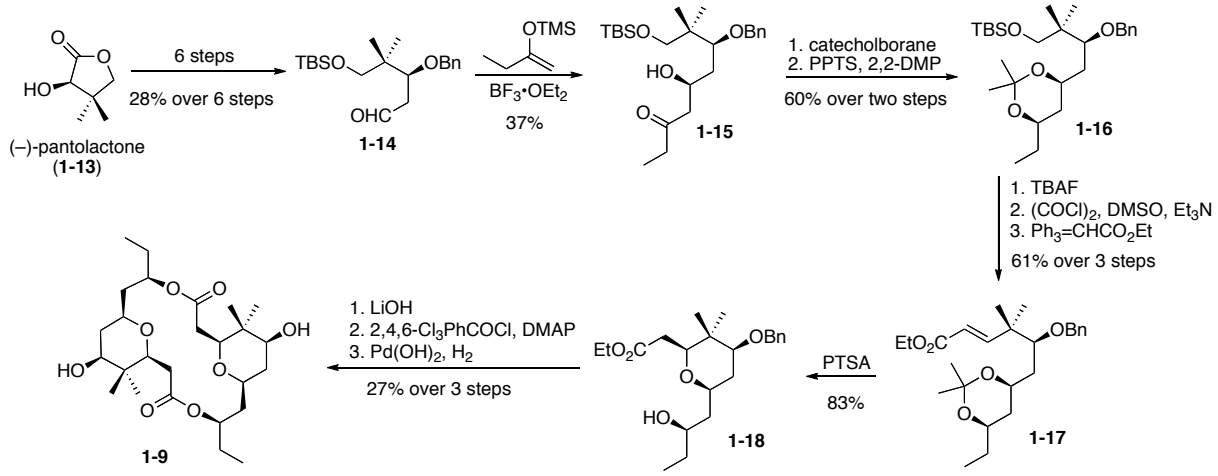
Scheme 1-2. Hong's second-generation synthesis of cyanolide A (**1-1**)



Reddy's Synthesis

Five months after Hong's publication, Reddy and co-workers reported a synthesis of cyanolide A starting from (–)-pantolactone (**1-13**) (Scheme 1-3).[10] (–)-Pantolactone was converted to aldehyde **1-14** through a previously reported six-step procedure.[11] A Mukaiyama aldol reaction of enolsilane and aldehyde **1-14** afforded **1-15** as a single diastereomer. Evan's cathecolborane-mediated *syn*-reduction[12] and subsequent acetonide formation resulted in **1-16**. TBAF deprotection of the TBS group followed by Swern oxidation and Horner-Wittig olefination furnished α,β-unsaturated ester **1-17**. Deprotection of the acetonide followed by an oxa-Michael cyclization in the presence of *p*-toluenesulfonic acid afforded *cis*-THP **1-18** as a single diastereomer. Ester hydrolysis of **1-18**, followed by subsequent dimerization using Yamaguchi's lactonization protocol,[13] and removal of the benzyl ether resulted in cyanolide A aglycon **1-9** in 16 steps with <1% overall yield.

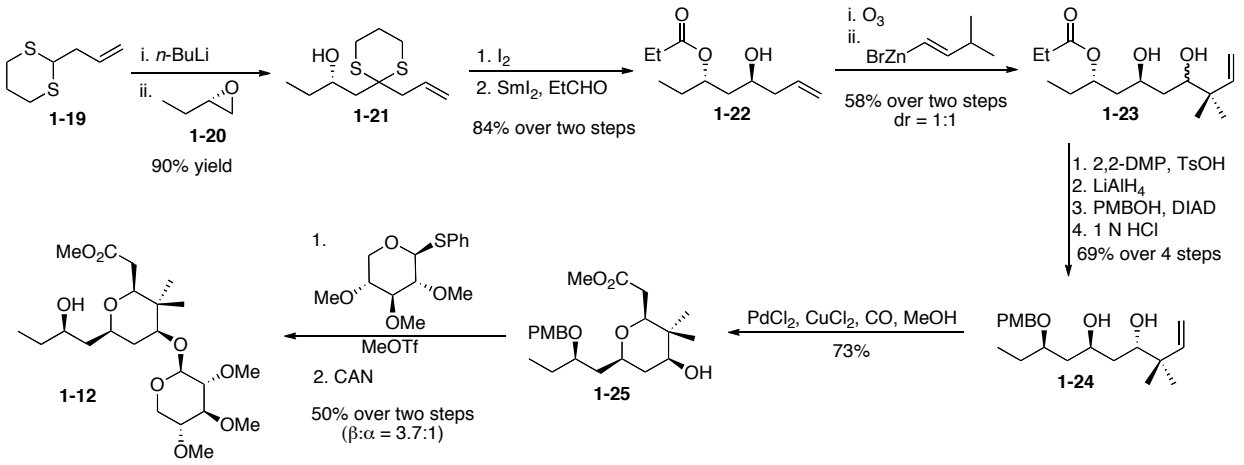
Scheme 1-3. Reddy's synthesis of cyanolide A aglycon **1-9**



She's Synthesis

In November of 2010, She and co-workers published a synthesis of cyanolide A that featured a palladium-catalyzed intramolecular alkoxycarbonylation (Scheme 1-4).[14] The route began with the deprotonation of 2-allyl-1,3-dithiane **1-19** and addition into (*S*)-2-ethyloxirane **1-20** to furnish alcohol **1-21**. Removal of the 1,3-dithiane and a subsequent SmI_2-promoted Evans-Tishchenko reduction[15] afforded **1-22**. Ozonolysis of **1-22** followed by a Barbier-type prenylation[16] yielded diol **1-23** as a 1:1 mixture of diastereomers. 1,3-Diol **1-24** was obtained from **1-23** after three protection/deprotection steps and a Mitsunobu reaction with 4-methoxyphenol. Treatment of **1-24** with palladium(II) chloride in the presence of copper(II) chloride and carbon monoxide resulted in *cis*-THP **1-25** as a single diastereomer. Glycosylation of the alcohol and oxidative cleavage of the PMB group with cerium(IV) nitrate provided alcohol **1-12**, the same intermediate reported in Hong's second-generation synthesis of cyanolide A (**1-1**). Monomer **1-12** was synthesized in 11 linear steps with a 4% yield.

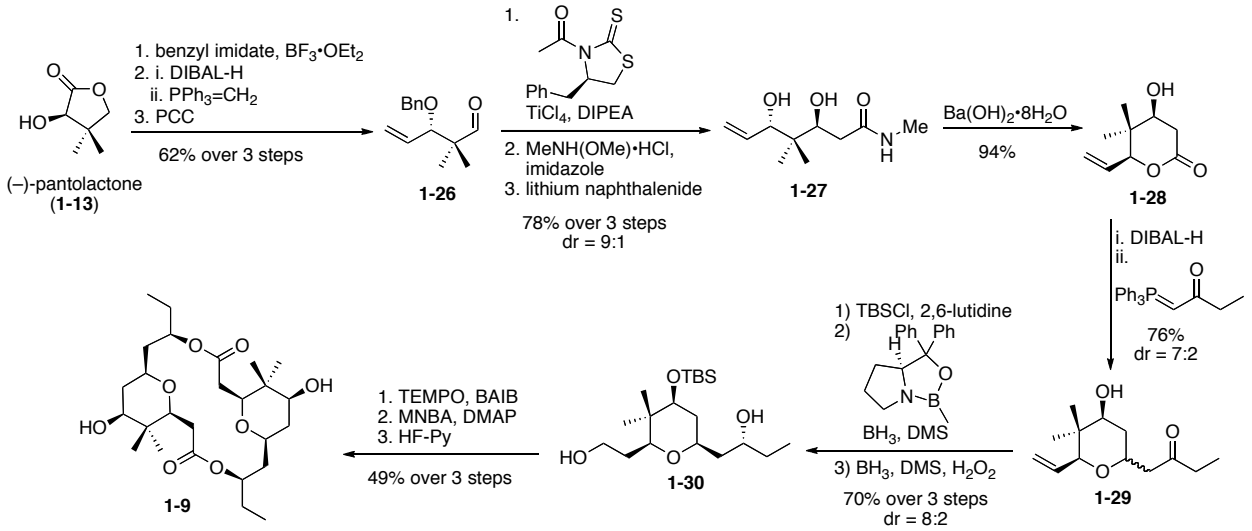
Scheme 1-4. She's formal synthesis of cyanolide A (**1-1**)



Pabbaraja's Synthesis

In December 2010, Pabbaraja and co-workers reported the fifth synthesis of cyanolide A (Scheme 1-5).[17] The synthesis began with (–)-pantolactone (**1-13**) similar to Reddy's approach. Benzyl protection of (–)-pantolactone (**1-13**), reduction of the lactone to the lactol, side chain extension via a Wittig reaction, and oxidation of the primary alcohol resulted in **1-26**. Aldehyde **1-26** was exposed to a Crimmin's acetate aldol reaction,[18] which proceeded with 9:1 diastereoselectivity. Formation of the Weinreb amide followed by debenzylation and cleavage of the N–O bond using lithium naphthalenide provided **1-27**. Treatment of alcohol **1-27** with $Ba(OH)_2 \bullet 8H_2O$ furnished lactone **1-28**. Reduction of the lactone to the lactol with DIBAL-H and a tandem Wittig olefination/oxa-Michael cyclization yielded THP **1-29** as a mixture of diastereomers. Protection of the alcohol with TBS, enantioselective reduction of the ketone with Corey's chiral borane catalyst,[19] and hydroboration/oxidation of the terminal olefin resulted in diol **1-30**. Selective oxidation of the primary alcohol to the carboxylic acid with TEMPO and BAIB, Shiina's lactonization previously used in Hong's syntheses of cyanolide A (**1-1**), and deprotection of the TBS group afforded cyanolide A aglycon **1-9**. This fourteen-step synthesis had an overall yield of 7%, but suffered from poor diastereoselectivity.

Scheme 1-5. Pabbaraja's synthesis of cyanolide A aglycon **1-9**

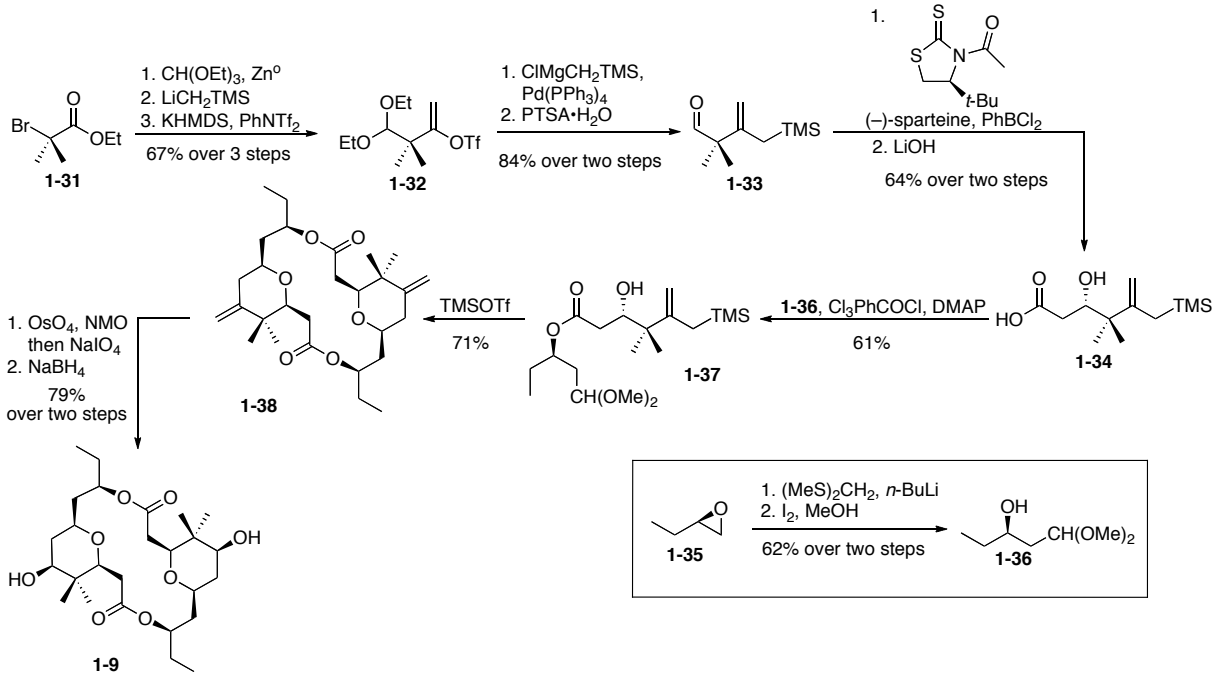


Rychnovsky's Synthesis

In May 2011, Rychnovsky and Gesinski published the first and only reported synthesis of cyanolide A that did not involve a lactonization to form the macrodiolide ring.[20] The macrodiolide was formed instead via a Sakurai macrocyclization/dimerization reaction. The route began with a Reformatsky-like addition of ethyl α-bromoisobutyrate (**1-31**) into triethyl orthoformate, mono-addition of an alkyllithium, and enol triflate formation of the resulting ketone to afford **1-32**.[21] Kumada coupling of enol triflate **1-32**, followed by deprotection of the acetal, provided aldehyde **1-33**. Sammakia's conditions,[22] utilizing dichlorophenylborane, afforded the desired aldol adduct as a single diastereomer and removal of the chiral auxiliary using lithium hydroxide furnished carboxylic acid **1-34**. Separately, alcohol **1-36** was synthesized in two steps by addition of dimethyl thioacetal to (*R*)-1,2-epoxybutane (**1-35**) followed by oxidation with iodine in the presence of methanol. Yamaguchi's esterification with alcohol **1-36** resulted in **1-37**.[23] A Sakurai dimerization/macrocyclization of **1-37** upon treatment with TMSOTf afforded macrodiolide **1-38**. A Lemieux–Johnson oxidation[24] of **1-38**, and subsequent reduction of the resulting ketone furnished cyanolide A aglycon **1-9**. The total

synthesis of the aglycon of cyanolide A was completed in eleven steps from **1-31** with a 12% overall yield.

Scheme 1-6. Rychnovsky synthesis of cyanolide A aglycon **1-9**

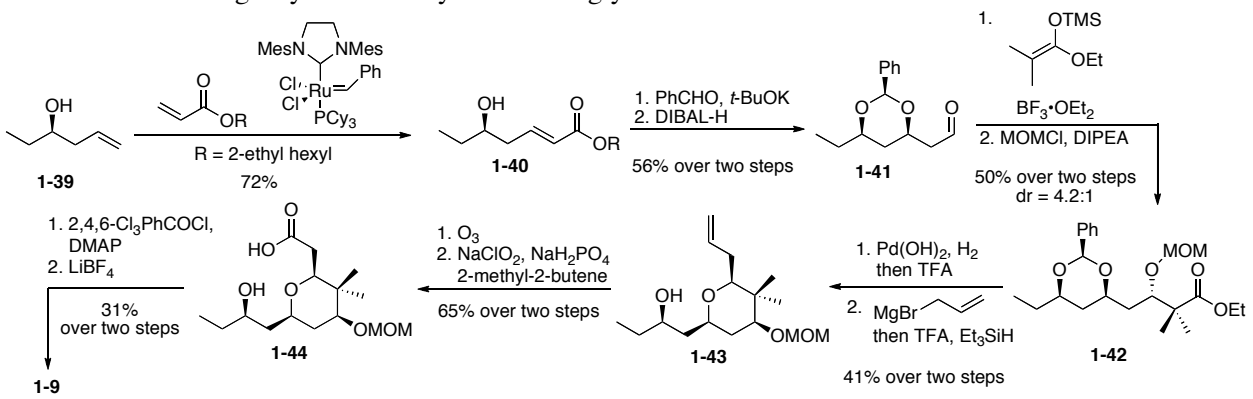


Jennings's Synthesis

Jennings and Sharpe published a synthesis of the aglycon in 2011 that featured a stereoselective Mukaiyama aldol reaction and oxocarbenium reduction (Scheme 1-7).[25] The route began with treatment of known alcohol **1-39**[26] with 2-ethylhexyl acrylate and Grubbs second-generation catalyst to form ester **1-40**. Methyl acrylate could be used in replacement of 2-ethylhexyl acrylate, but was not because of isolation and purification issues due to the low molecular weight of the desired product. A tandem hemiketal formation/intramolecular hetero-Michael addition followed by reduction of the ester afforded aldehyde **1-41**. A Mukaiyama aldol reaction with *gem*-dimethyl silyl ketene acetal and subsequent MOM protection of the resulting alcohol provided **1-42** as a mixture of diastereomers. Treatment of

1-42 with H_2 and Pearlman's catalyst, $Pd(OH)_2$, afforded the diol, which immediately underwent lactonization when treated with trifluoroacetic acid (TFA). Allylmagnesium bromide addition to the new ester moiety and tandem stereoselective oxocarbenium cation formation/reduction with TFA and Et_3SiH afforded THP **1-43**. Oxidation of the terminal olefin resulted in monomer **1-44**. Dimerization of **1-44** under Yamaguchi macrocyclization conditions similar to those used in Reddy's synthesis, and deprotection of the MOM group with $LiBF_4$ furnished cyanolide A aglycon **1-9**. The total synthesis of the aglycon of cyanolide A was completed in eleven steps with <1% overall yield.

Scheme 1-7. Jennings' synthesis of cyanolide A aglycon **1-9**

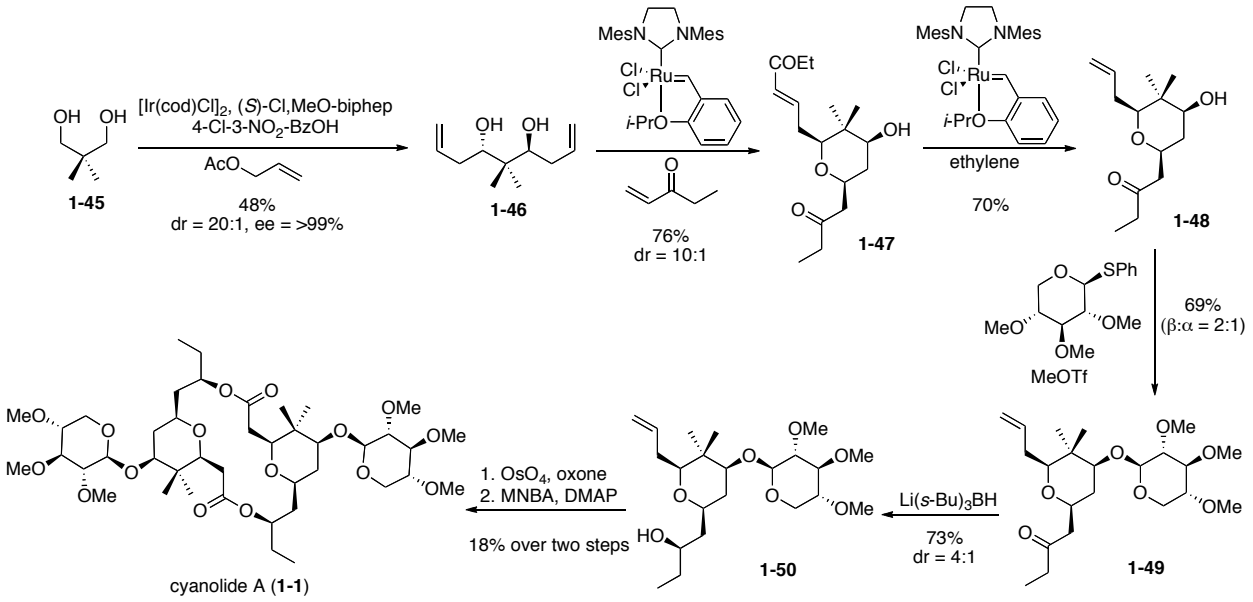


Krische's Syntheses

In 2013, Krische and Waldeck published the shortest synthesis of cyanolide A to date (Scheme 1-8).[27] The synthesis began with a diastereoselective double allylation of **1-45** using $[Ir(cod)Cl]_2$, allyl acetate, 4-chloro-3-nitrobenzoic acid, and chiral ligand (*S*)-Cl,MeO-biphep. Conversion of **1-46** under Fuwa's cross-metathesis/oxa-Michael cyclization cascade conditions[28] afforded **1-47** in a 10:1 diastereomeric ratio. THP **1-47** underwent cross-metathesis with ethylene in the following step to yield **1-48**. Glycosylation of THP **1-48** using Hong's conditions afforded **1-49**, and diastereoselective reduction of ketone **1-49** resulted in monomer **1-50**. Oxidative

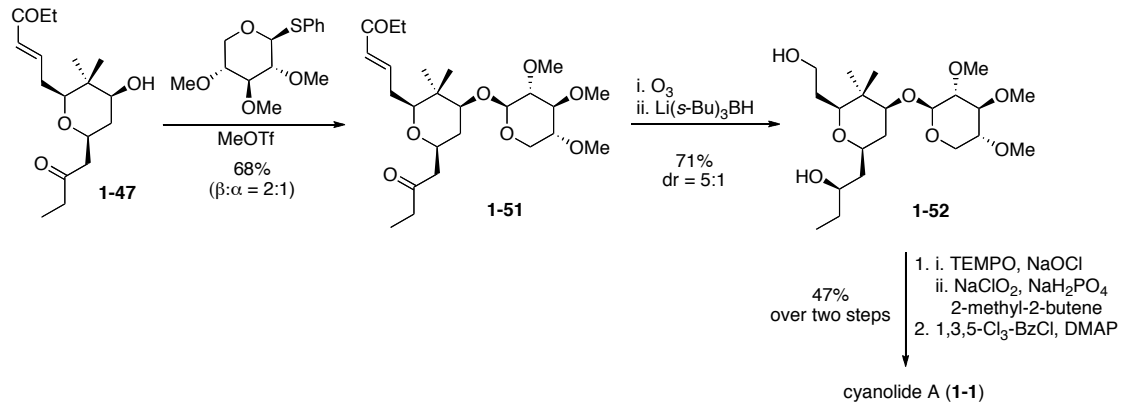
cleavage of the terminal olefin provided the carboxylic acid and subsequent dimerization, under Shiina's conditions, afforded cyanolide A (**1-1**) in seven linear steps.

Scheme 1-8. Krische's first-generation synthesis of cyanolide A (**1-1**)



Krische and Waldeck simultaneously reported a slightly shortened second-generation route, reducing the step count even further to six linear steps (Scheme 1-9). Intermediate **1-47** was glycosylated using the same conditions as in the first-generation route to afford glycoside **1-51**. Ozonolysis of **1-51** followed by treatment with excess Li(*s*-Bu)$_3$BH furnished diol **1-52**. Selective oxidation of the primary alcohol to the carboxylic acid, and subsequent macrodiolide formation under conditions reported by Yamaguchi and co-workers[23] resulted in the total synthesis of cyanolide A in only six steps from neopentyl glycol (**1-45**) in a 4% overall yield.

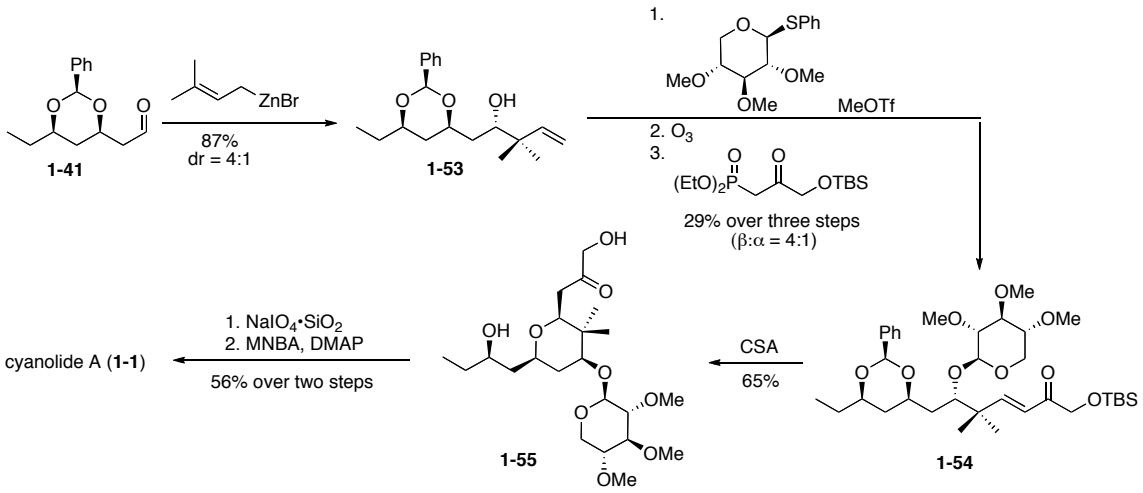
Scheme 1-9. Krische's second-generation synthesis of cyanolide A (**1-1**)



Bates's Synthesis

Following the publication of the synthetic route to be discussed in this chapter, Bates and Lek reported the eleventh synthesis (including second-generation syntheses) of cyanolide A (**1-1**) (Scheme 1-10).[29] The route began with the same intermediate used in Jennings' synthesis of cyanolide A, aldehyde **1-41**. A Barbier-type prenylation onto the aldehyde, similar to She's synthesis, yielded alcohol **1-53** as a 4:1 mixture of diastereomers. After examining a variety of glycosylation conditions, Bates and Lek returned to the same conditions described in Hong's original report. Ozonolysis of the terminal olefin, followed by a Horner-Wadsworth-Emmons reaction, afforded enone **1-54**. Removal of the benzylidene acetal followed by an oxa-Michael cyclization in the presence of a Brønsted acid, comparable to Reddy's approach, furnished *cis*-THP **1-55**. Cleavage of the α-hydroxy ketone with sodium periodate and Shiina macrocyclization resulted in cyanolide A (**1-1**). This route is seven linear steps long starting from known intermediate **1-41** with a 6% overall yield.

Scheme 1-10. Bates' synthesis of cyanolide A (**1-1**)



Retrosynthetic Analysis

A modular synthesis to construct **1-1**, as well as strategic derivatives was devised in order to determine the structural features of cyanolide A (**1-1**) required for molluscicidal activity. The biological testing was done in collaboration with Gerwick and co-workers. Preliminary studies with cyanolide A aglycon **1-9** and MEM ether **1-56** (which could mimic the solubility properties of the xylose moiety) showed no molluscicidal activity (Figure 1-4).[30] This suggests that the xylose moiety is necessary for molluscicidal activity. When (+)-xylose (**1-57**) was screened independently, it showed no activity against *Biomphalaria glabrata*; therefore, we concluded that both the xylose moiety and tetrahydropyran-containing (THP) core must be present for molluscicidal activity.

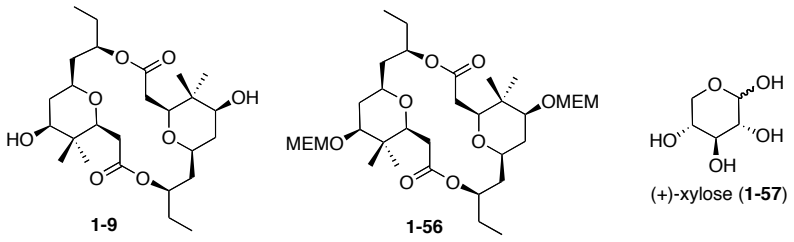
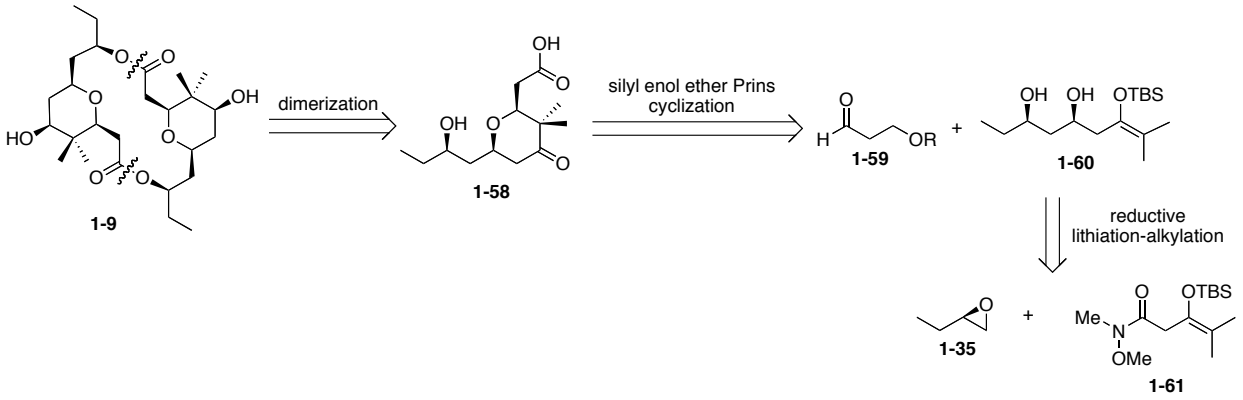


Figure 1-4. Initial substrates tested for molluscicidal activity

A modular route to cyanolide A aglycon **1-9** would allow for facile access of both cyanolide A and its analogues. The approach described herein relied on a late-state Shiina macrocyclization of tetrahydropyranone (THPO) **1-58**, as seen in Hong's synthesis, to access cyanolide A aglycon **1-9** (Scheme 1-11). The THPO (**1-58**) would be formed via a silyl enol ether Prins cyclization between diol **1-60** and aldehyde **1-59**. Diol **1-60** would be prepared from reductive alkylation of Weinreb amide **1-61**.

Scheme 1-11. Retrosynthetic analysis of cyanolide A aglycon **1-9**

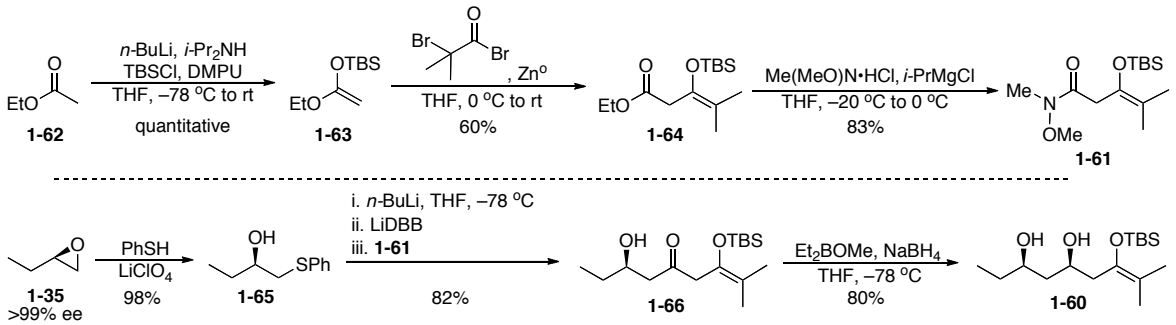


Results and Discussion

The synthetic route toward cyanolide A aglycon **1-9** utilizes a late-stage silyl enol ether Prins cyclization between aldehyde **1-59** and diol **1-60**. The synthesis of diol **1-60** was devised by Dr. Michael Gesinski as part of an abandoned route towards **1-9**.[31] Preparation of diol **1-60** commenced with the formation of silyl ketene acetal **1-63** from ethyl acetate (**1-62**) (Scheme 1-12). Zinc reduction of α-bromoisobutyryl bromide produced a disubstituted ketene in situ that when reacted with silyl ketene acetal **1-63**, afforded ethyl ester **1-64**.[32] Weinreb amide **1-61** was formed directly from ester **1-64** in good yield.[33] Separately, enantiopure epoxide **1-35**[34] was subjected to ring opening using thiophenol to obtain *β*-thiophenyl alcohol **1-65**. *β*-Thiophenyl alcohol **1-65** was deprotonated with *n*-butyllithium before being reduced with lithium

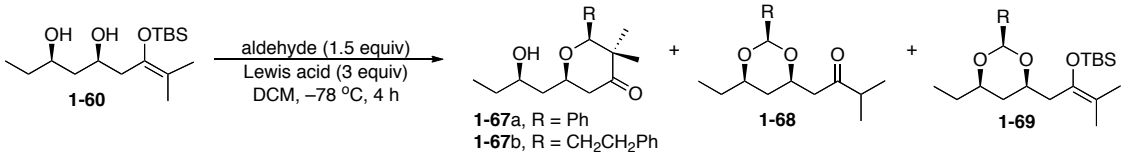
di-*tert*-butylbiphenylide (LiDBB). The resulting alkyllithium reagent was reacted with Weinreb amide **1-61** to afford ketone **1-66**.[35] Ketone **1-66** was then reduced under Narasaka's conditions[36] to afford *syn*-diol **1-60**.

Scheme 1-12. Synthesis of diol **1-60**



With diol **1-60** in hand, attention was then turned toward testing the viability of the silyl enol ether Prins reaction to form tetrasubstituted THPO rings, such as THPO **1-58** (Scheme 1-11). A series of Lewis acids were examined using both aromatic and aliphatic aldehydes as model systems (Table 1-1). The cyclization of diol **1-60** was first tested using a model aromatic aldehyde, benzaldehyde, to form THPO **1-67**a. It was found that boron trifluoride etherate was optimal for this transformation (64% yield, entry 1). However, when switching to aliphatic aldehyde, dihydrocinnamaldehyde, boron trifluoride etherate was ineffective (entry 4). After testing a range of Lewis acids, the highly reactive trimethylsilyl triflate (TMSOTf) provided the highest yield (55%, entry 13) for the desired THPO **1-67**b. Formation of dioxanes **1-68** and **1-69** by diol protection was observed in certain cases (entries 4, 5, and 6). Desired THPO **1-67** was formed as a single diastereomer in all cases. The hypothesized mechanism for the silyl enol ether Prins cyclization is discussed in detail in Chapter 2.

Table 1-1. Silyl enol ether Prins cyclization of diol **1-60** and an aldehyde with varying Lewis acids

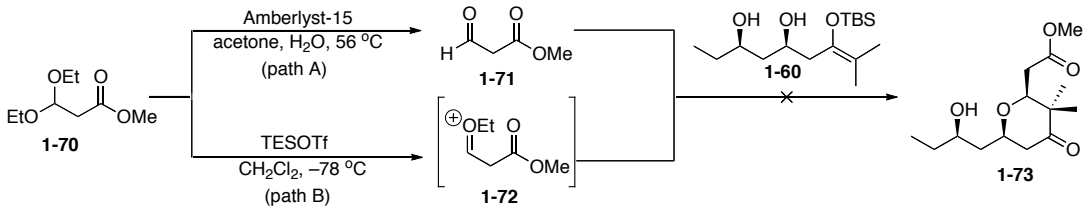


entry	Lewis acid	R	1-67	1-68	1-69
1[a]	BF_3•OEt_2	Ph	64%	-	-
2[a]	TESOTf	Ph	54%	-	-
3[a]	$TiCl_4$	Ph	<5%	-	-
4[a]	BF_3•OEt_2	CH_2CH_2Ph	-	20%	-
5[a]	$Sc(OTf)_3$	CH_2CH_2Ph	-	-	7%
6[a]	$Yb(OTf)_3$	CH_2CH_2Ph	-	-	<5%
7[a]	$TiCl_4$	CH_2CH_2Ph	<5%	-	-
8[a]	TESOTf	CH_2CH_2Ph	10%	-	-
9	Et_2AlCl	CH_2CH_2Ph		no rxn	
10	$TiBr_4$	CH_2CH_2Ph		decomposition	
11	$MgBr_2$•OEt_2	CH_2CH_2Ph		no rxn	
12[b]	$SnCl_4$	CH_2CH_2Ph	14%	-	-
13[a]	TMSOTf	CH_2CH_2Ph	55%	-	-

[a]isolated yields, [b]yields determined by ^{1}H NMR spectroscopy with respect to nitromethane internal standard.

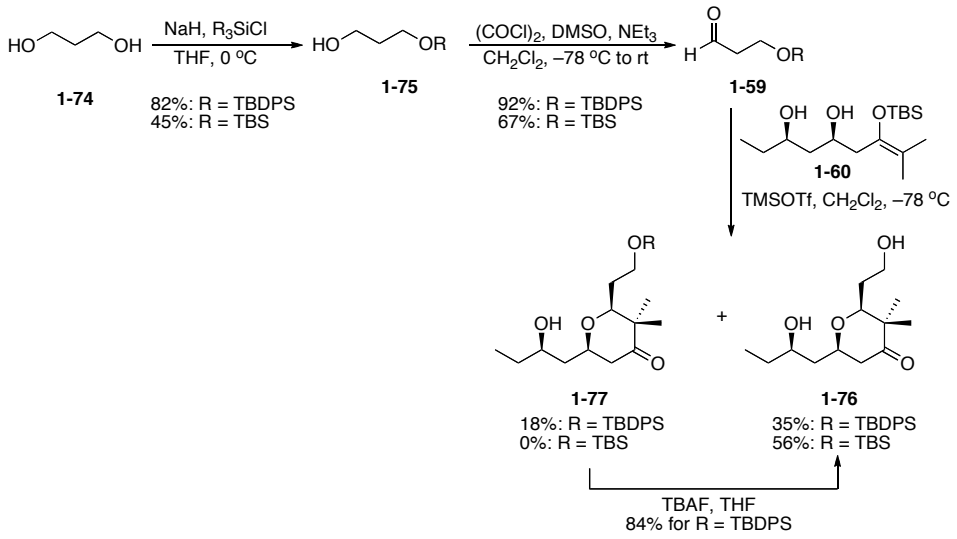
Based on the results of the silyl enol ether Prins model system, cyclization of diol **1-60** with aldehyde **1-71** was attempted (Scheme 1-13). The cyclization was envisioned to provide THPO **1-73**, which, after a series of steps (hydrolysis, dimerization, and reduction), would provide aglycon **1-9**. Aldehyde **1-71** was reported to form in situ when acetal **1-70** was refluxed with Amberlyst-15 and water.[37] Attempts to isolate and purify aldehyde **1-71** to ensure its formation for use in the silyl enol ether Prins cyclization led to decomposition of **1-71** (path A). Attention was then turned toward in situ generation of the oxocarbenium ion **1-72** from acetal **1-70** followed by addition of diol **1-60** to afford THPO **1-73** (path B). No desired product was obtained; it is hypothesized that proposed oxocarbenium ion intermediate **1-72** was deprotonated to give the unreactive ethyl vinyl ether.

Scheme 1-13. Attempted silyl enol ether Prins reaction starting with acetal **1-70**



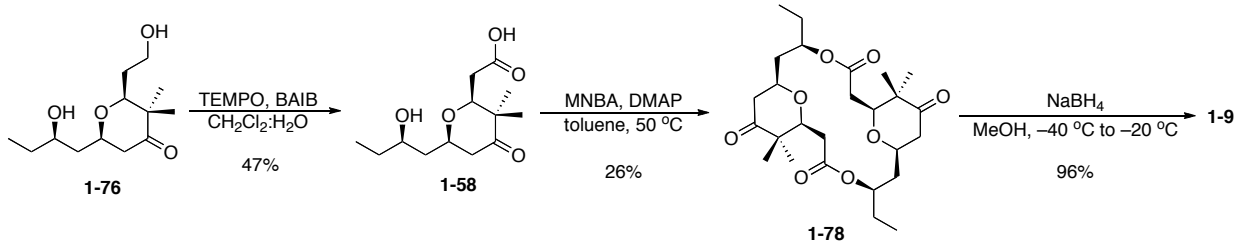
Because formation of THPO **1-73** was not achieved from the silyl enol ether Prins cyclization starting from acetal **1-70**, aldehyde **1-59** was then examined as an alternate cyclization partner (Scheme 1-14). The synthesis of aldehyde **1-59** began with the mono-protection of 1,3-propanediol (**1-74**) with *tert*-butyldiphenylsilyl chloride (TBDPSCl) to afford alcohol **1-75**.[38] Subsequent Swern oxidation of **1-75** provided aldehyde **1-59** in good yield.[39] Exposure of aldehyde **1-59** to diol **1-60** in the presence of excess trimethylsilyl triflate promoted a silyl enol ether Prins cyclization and in situ deprotection of the TBDPS group to yield a mixture of tetrahydropyranone **1-76** (35%) and **1-77** (18%). Deprotection of **1-77** with tetra-*n*-butylammonium fluoride (TBAF) resulted in THPO **1-76**. Interestingly, treatment of the crude cyclization reaction mixture with TBAF did not increase the amount of THPO **1-76** isolated. Further optimization with different Lewis acids ($CeCl_3$, Ti(O*i*-Pr)$_4$, (*n*-Bu)$_2$Sn(OTf)$_2$, $SiCl_4$/HMPA, Ga(OTf)$_3$) did not improve cyclization yields. However, changing the silyl group on aldehyde **1-59** from TBDPS to the more acid sensitive TBS group[40] increased the yield of **1-76** to 56%. Addition of a nonnucleophilic base, 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), to buffer the reaction mixture from the formation of trifluoromethanesulfonic acid did not improve the desired product yield, but did change the ratio of THPO **1-76** and **1-77** formed, favoring protected THPO **1-77**.

Scheme 1-14. Synthesis of THPO **1-76**



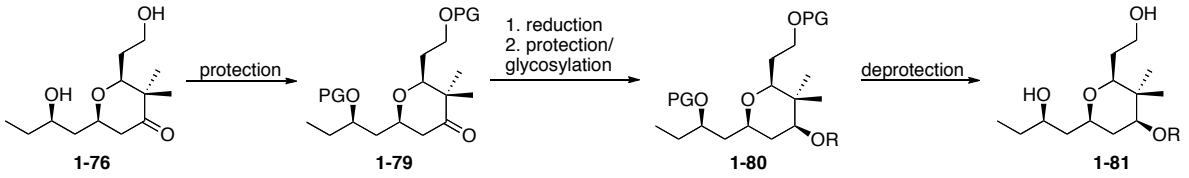
Selective oxidation of the primary alcohol on THPO **1-76** to the carboxylic acid proved challenging owing to possible under-oxidation and over-oxidation of the alcohols.[41] Optimized TEMPO oxidation conditions with [bis(acetoxy)iodo]benzene successfully afforded carboxylic acid **1-58** (Scheme 1-15).[17,42] It was hypothesized that macrocyclization of **1-58**, followed by reduction of macrocycle **1-78**, carried out in accordance with Hong's report would result in cyanolide A aglycon **1-9**.[8,9] Unfortunately, macrocyclization of **1-58** using Shiina's lactonization conditions provided a complex mixture of products. In order to decrease the amount of oligomerization, the reaction temperature was lowered from 90 °C[8] to 50 °C, and the addition time of carboxylic acid **1-58** was increased. The desired macrocycle (**1-78**) was only ever obtained in low yields, even after optimization.

Scheme 1-15. Synthesis of cyanolide A aglycon **1-9**



The low yielding macrocyclization of **1-58** indicated that the ketone on the THPO ring may be interfering with the lactonization because successfully macrocyclization have been performed on substrates similar to carboxylic acid **1-58**, albeit with a protected ketone or an alcohol instead of a ketone on the ring.[8,10,17,25,27] THPO **1-76** was reduced prior to TEMPO oxidation and macrocyclization in an effort to remove the problematic ketone. Unfortunately, macrocyclization attempts with the free alcohol on the THP provided decomposition with no desired cyanolide A aglycon **1-9** observed. In order to increase the yield of the macrocyclization, reduction of the ketone on THPO **1-76** and subsequent protection of the forming alcohol was explored. Protection of diol **1-76** followed by reduction of ketone **1-79** and protection/glycosylation of the resulting secondary alcohol afforded THP **1-80** (Scheme 1-16). Removal of the protecting groups on both exocyclic alcohols resulted in diol **1-81** which could then undergo the same oxidation/macrocyclization route as diol **1-76** in Scheme 1-15.

Scheme 1-16. Synthesis of diol **1-81** to remove the problematic ketone functional group.

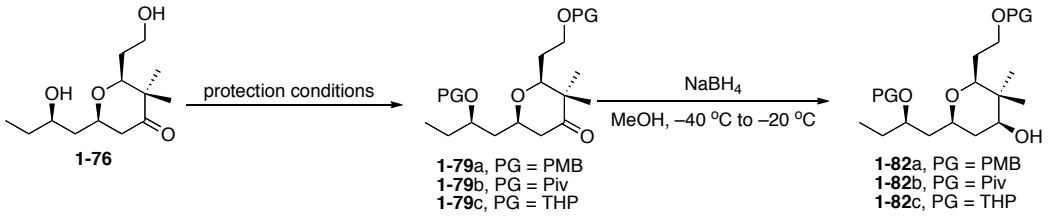


1-76 **1-79** **1-80** **1-81**

Pivalate, PMB, and THP protecting groups on **1-79** were examined in order to obtain substrates similar to known literature examples[8,17] as well as to explore different late stage glycosylation routes. Ketone **1-79**a (Table 1-2) is closely related to one of Hong's substrates (Scheme 1-2, compound **1-10**) that underwent glycosylation with methylated (+)-xylose.[8] Ketone **1-79**b was subjected to microwave glycosylation with acetylated (+)-xylose. Both glycosylations will be discussed in further detail later on in the chapter. Further manipulation of ketone **1-79**c resulted in known compound **1-30** (Scheme 1-5), thereby completing the formal synthesis of

cyanolide A.[17] Screening different PMB protection conditions revealed that diol **1-76** was sensitive to strong bases (Table 1-2, entries 1–4). It was hypothesized that deprotonation of the secondary alcohol provided an alkoxide that could then deprotonated alpha to the ketone, going through a six membered transition state; formation of the enolate then led to decomposition of diol **1-76**. Ketone **1-79**a was successfully obtained through treatment of **1-76** with PMB-trifluroimidate and PPTS (entry 5). Yields were moderate because of sluggish protection of the secondary alcohol; after 48 hours, there was a mixture of mono and bisprotected product. Monoprotection was a common issue, also occurring when diol **1-76** was stirred with PivCl (entry 6), resulting in only 12% yield of **1-79**b. Protection of diol **1-76** with a dihydropyran gave a mixture of diastereomers that were carried through without separation (entry 7). Reduction of ketones **1-79**a–c to corresponding alcohols **1-82**a–c proceeded without complication. Due to conformational bias of the THPO ring, alcohols **1-82**a–c were obtained as a single diastereomer.

Table 1-2. Protection and reduction of diol **1-76**



1-76

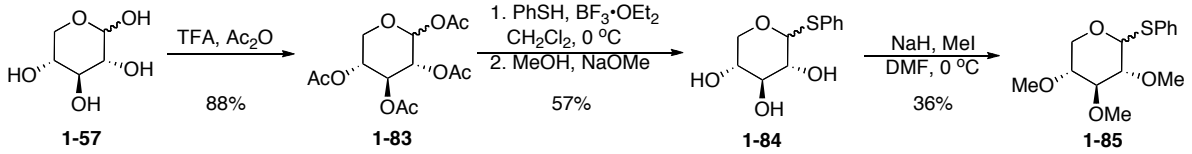
1-79a, PG = PMB
1-79b, PG = Piv
1-79c, PG = THP

1-82a, PG = PMB
1-82b, PG = Piv
1-82c, PG = THP

entry	protection conditions			protection yield	reduction yield
	Base/Acid	Additive	PG-X		
1	NaH		PMB-Cl	decomposition	
2	NaH	TBAI	PMB-Cl	decomposition	
3	*t*-BuOK		PMB-Br	decomposition	
4	TfOH		PMB-O, CF_3, NH	decomposition	
5	PPTS		PMB-O, CF_3, NH	45%	82%
6	pyridine		PivCl	12%	90%
7	PPTS		O	64%	92%

Concurrent with the synthesis of cyanolide A (**1-1**), the glycosylation of THP rings and monomeric cyanolide A aglycon analogues were investigated in order to gain insight on the structure activity relationship of cyanolide A. The glycosylation precursor, thioether **1-85**, was obtained in four steps from (+)-xylose (**1-57**) (Scheme 1-17). (+)-Xylose (**1-57**) was acetyl-protected to afford tetra-*O*-acetyl-D-xylopyranose (**1-83**).[43] Treatment of **1-83** with thiophenol and boron trifluoride etherate, followed by hydrolysis of the acetate groups, furnished triol **1-84**.[44] Triol **1-84** was methylated with sodium hydride and methyl iodide to afford thioether **1-85**.[43,45]

Scheme 1-17. Synthesis of thioether **1-85**



With thioether **1-85** in hand, THPs **1-86**–**1-89** were synthesized as the first batch of compounds to be tested for molluscicidal activity (Figure 1-5a). Tetrahydropyrans **1-86** and **1-87**, analogues of the monomer of cyanolide A (**1-1**) (Figure 1-5b), were obtained in three steps from THPO **1-67**a, a product of the silyl enol ether Prins reaction model system. The synthesis of THP substrates **1-86** and **1-87** commenced with acetylation of THPO **1-67**a (Scheme 1-18) followed by reduction of ketone **1-90** with $NaBH_4$. Glycosylation of alcohol **1-91** with thioether **1-85** using Hong's conditions afforded THF **1-86** and **1-87**.[8] Tetrahydropyran substrates **1-88** and **1-89** were obtained from glycosylation of THP compounds previously synthesized in the Rychnovsky group.[46] The Gerwick group tested glycosylation products **1-86**–**1-89** for molluscicidal activity and found that only **1-88** showed activity (LC_{100} = 106 μM). These results suggested that the β-anomer was necessary for molluscicidal activity.

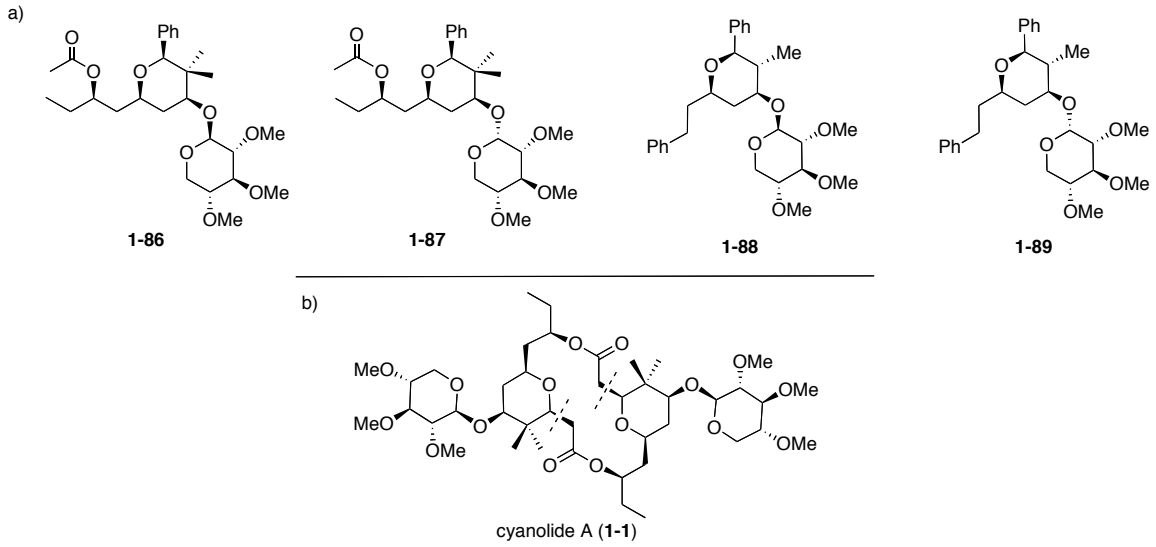
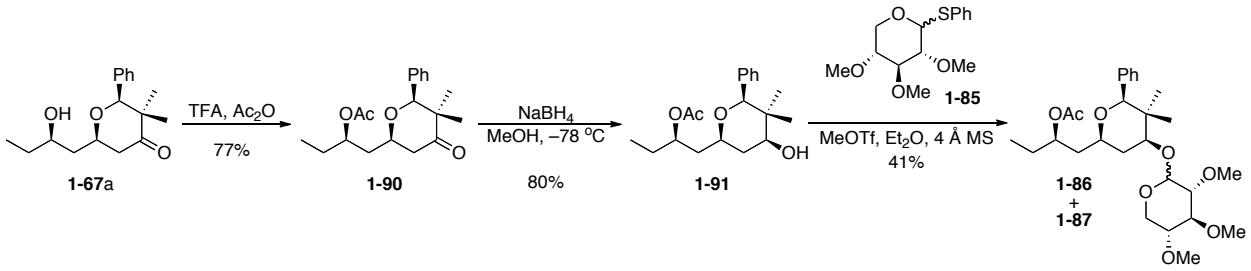


Figure 1-5. (a) First batch of glycosylated model systems to be tested for molluscicidal activity. (b) Cyanolide A (**1-1**) shown with possible dimerization bond disconnection to obtain cyanolide A monomer.

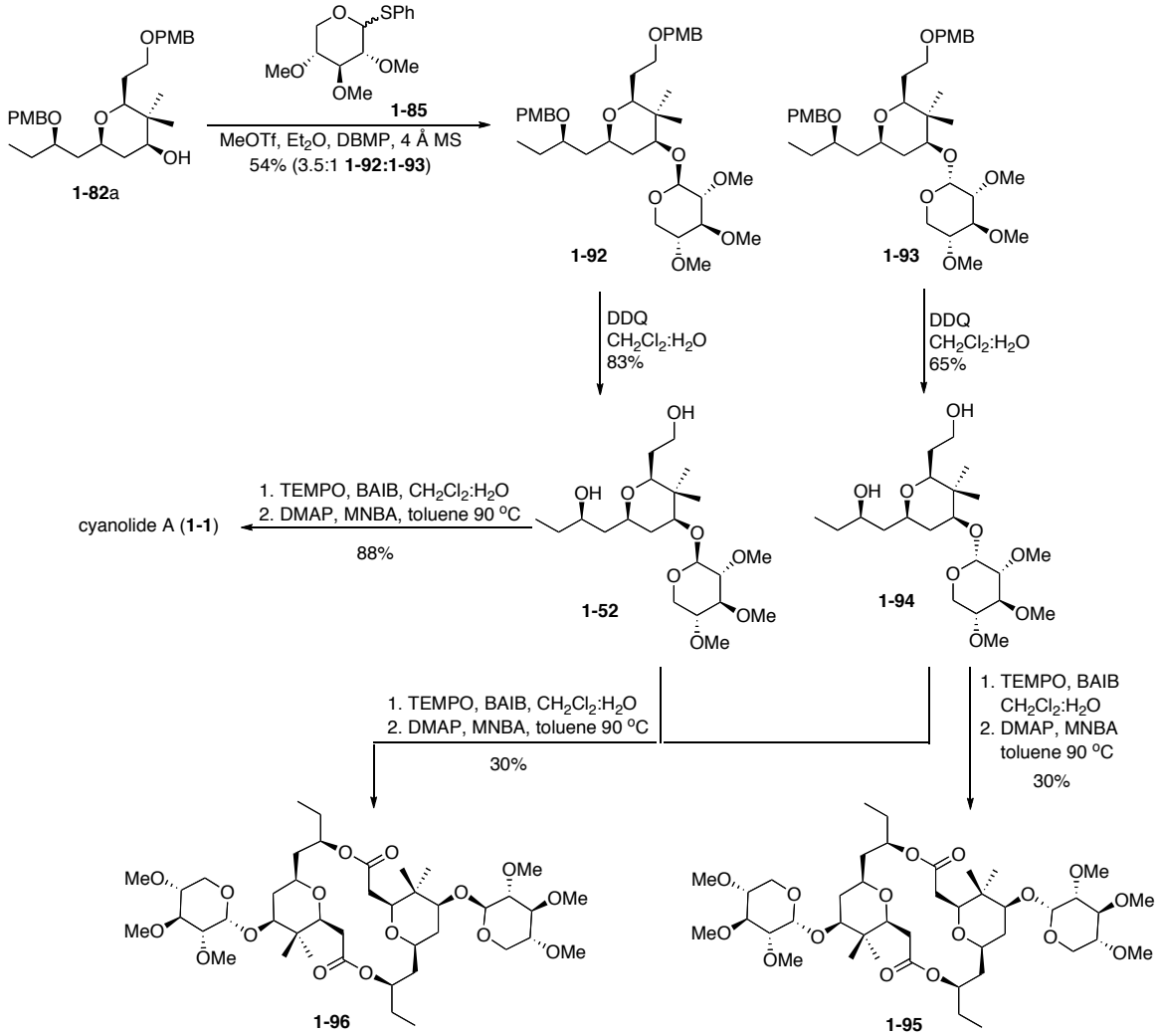
Scheme 1-18. Synthesis of THP (*S*)-**1-86** and THP (*R*)-**1-87**.



Glycosylation with thioether **1-85** under Hong's conditions was slow and low yielding, and the resulting mixture of compounds were difficult to separate. It was found that the reaction was extremely moisture sensitive, therefore, reactions were set up in a glovebox and carried out in a Teflon sealed vial placed within a sealed secondary container. Yields were further improved with the addition of DBMP, buffering the reaction mixture from the formation of trifluoromethanesulfonic acid. Alcohol **1-82**a was glycosylated in a 54% yield (3.5:1 β:α ratio) (Scheme 1-19). The resulting glycosides **1-92** and **1-93** were separated and deprotected with

2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). TEMPO oxidation of the primary alcohol in THP **1-52** followed by macrocyclization afforded cyanolide A (**1-1**). Treatment of THP **1-94** under the same conditions resulted (α:α)-anomer **1-95**, while a mixture of THPs **1-52** and **1-94** afforded a mixture of anomers with (α:β)-anomer **1-96** was isolated in 30% yield.

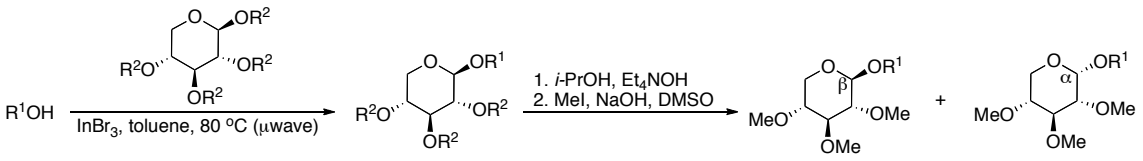
Scheme 1-19. Synthesis of cyanolide A (**1-1**) and corresponding (α:α)-**1-95** and (α:β)-**1-96** anomers

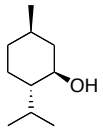
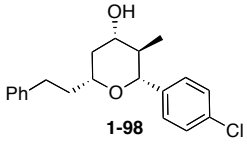
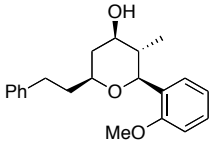
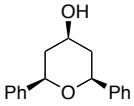


Other sugars with neighboring directing groups were explored to enhance the β-selectivity of the glycosylation. Glycosylation of a bulky alcohol, menthol (**1-97**), with sugar **1-83** using microwave conditions developed by Polt afforded glycoside **1-101** (Table 1-3).[47] The

reaction times were shorter (1 min), and the resulting mixture was cleaner than those run under the original glycosylation conditions with thioether **1-85**. The yields vastly improved, and the diastereomers were easy to separate. The β-selectivity of the glycosylation was found to improve when the acetate groups were exchanged for bulkier pivalate groups, sugar **1-102**. THP compounds **1-98**–**1-100**, previously synthesized in the Rychnovsky group, were glycosylated with sugar **1-102**.[46] The yields for compounds **1-104**–**1-106** were lower than glycoside **1-103** and the β-selectivity varied drastically, suggesting this glycosylation method is very substrate dependent. While it was envisioned that this reaction could be more effective with a well-matched substrate, two more synthetic steps (deprotection and methylation) are required after glycosylation in order to achieved the desired methylated (+)-xylose glycoside. Nonetheless, the ester-protected intermediates could also be screened by Gerwick's group for molluscicidal activity as sugar derivatives, along with the methylated product. The mild deprotection and methylation steps occur in considerably higher yields with the breaking and forming of six bonds.[48] Previously mentioned alcohol **1-82**b (Table 1-2) could be glycosylated with sugar **1-83**. Selective deprotection of the acetyl groups followed by further functionalization could yield cyanolide A (**1-1**). This route was abandoned, however, when the glycosylation reaction using Hong's conditions was optimized.

Table 1-3. Microwave glycosylation and further manipulations to the desired methylated (+)-xylose glycoside



R^1OH	R^2	glycosylation yield	deprotection/methylatation yield
 **1-97**	Ac (**1-83**)	86% (**1-101**) 3:1 β:α ratio	41% (**1-107**)
	Piv (**1-102**)	88% (**1-103**) 10:1 β:α ratio	
 **1-98**	Piv (**1-102**)	35% (**1-104**) 1.5:1 β:α ratio	63% (**1-108**)
 **1-99**	Piv (**1-102**)	34% (**1-105**) >95:5 β:α ratio	87% (**1-109**)
 **1-100**	Piv (**1-102**)	44% (**1-106**) >95:5 β:α ratio	—

Glycoside **1-92**a**,** cyanolide A (**1-1**), α,α-isomer **1-95**, α,β-isomer **1-96**, and glycosides **1-104**–**1-109** were tested by the Gerwick group for molluscicidal activity. Through multiple trials, it was discovered that synthetic cyanolide A did not exhibit the same biological activity reported for the naturally occurring sample, even though these two materials are identical by standard characterization techniques[49]. Naturally occurring cyanolide A was repurified via reverse phase preparatory HPLC.[50] Cyanolide A (**1-1**) eluted between 24 and 25 minutes. All fractions were collected and tested for molluscicidal activity. Interestingly, the fraction that eluted at 23 minutes showed the same molluscicidal activity that was reported in Gerwick's original isolation paper but the fractions that eluted at 24 and 25 minutes, which contained cyanolide A, did not have any molluscicidal activity. It is suspect that an undetectable quantity of

impurity is present in the naturally occurring sample of cyanolide A which is responsible for the original pesticidal activity reported. Unfortunately, the amount of isolated material was not enough to confirm the identity of the impurity and the cyanobacteria that cyanolide A was originally isolated from could not be easily obtained again.

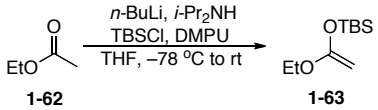
Conclusion

The synthesis of cyanolide A (**1-1**) was completed with a longest linear sequence of twelve steps with an overall 2% yield. All stereocenters in the molecule are set from the enantiomerically enriched epoxide, with no chiral auxiliaries necessary. Two other syntheses were developed for the formal synthesis of cyanolide A and cyanolide A aglycon **1-9** by varying late stage steps. A variety of cyanolide A analogues were synthesized to determine the structure-activity relationship (SAR). It was discovered that cyanolide A was not responsible for the biological activity originally reported in the isolation paper by Gerwick's group, but instead a small impurity may be responsible for the activity observed. The Gerwick group is currently in the process of identifying the structure of this impurity, which they reason will be a highly potent molluscicide.

General Information. All air- and moisture-sensitive reactions were carried out in flame- or oven-dried flasks equipped with a magnetic stir bar under an argon atmosphere. All commercially available reagents were used as received unless stated otherwise. Tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, and dichloromethane (CH_2Cl_2), were passed through two 4 × 36 inch columns of anhydrous neutral alumina A-2 (8 × 14 mesh, LaRoche Chemicals; activated under a flow of Ar 350 °C for 12 h) to remove H_2O according to the procedure described by Grubbs.[51] Zinc dust was activated by sequential washing with 1 M HCl, water, and ethanol and was then dried under reduced pressure. $BF_3{\cdot}OEt_2$ was distilled neat under argon atmosphere. TMSOTf was distilled over CaH_2 under reduced pressure. (*R*)-1,2-Epoxybutane **1-35** was prepared according to published procedures.[34] Thin-layer chromatography (TLC) was performed on 250 μm layer silica gel plates, and developed plates were visualized by UV light, *p*-anisaldehyde, potassium permanganate, vanillin, phosphomolybdic acid, or 2,4-dinitrophenylhydrazine.

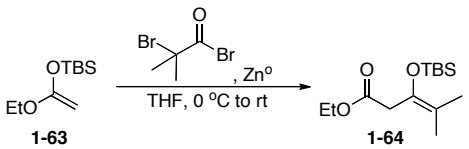
^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra were recorded at 126 MHz. Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent, br. = broad), coupling constant(s) in Hertz (Hz), and integration. Infrared spectra were recorded on NaCl plates. High resolution mass spectrometry was performed using ESI-TOF.

Procedures and Characterization



1-62 **1-63**

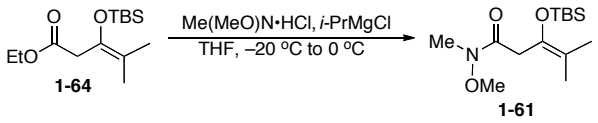
***tert*-Butyl(1-ethoxyvinyloxy)dimethylsilane (1-63).** A solution of *n*-butyllithium (25 mL, 56 mmol, 2.2 M in hexanes) was added dropwise to a solution of distilled diisopropylamine (8.6 mL, 61 mmol) in THF (125 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and cooled to –78 °C. Ethyl acetate (5.0 mL, 51 mmol) was added dropwise over 10 min at –78 °C. After 1 h, DMPU (10.4 mL, 86.5 mmol) was added dropwise followed by a solution of *tert*-butyldimethylsilyl chloride (9.2 g, 61 mmol) in THF (10 mL). After 30 min at –78 °C, the reaction mixture was warmed to room temperature over 1 h and concentrated *in vacuo*. The suspension was diluted with pentanes (200 mL) and washed successively with H_2O (200 mL), saturated aqueous $CuSO_4$ (200 mL), and saturated aqueous $NaHCO_3$ (200 mL). The aqueous layers were back-extracted with pentanes (100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford silyl ketene acetal **1-63** as a clear yellow oil (10.3 g, quant.). ^1H and ^{13}C NMR spectra matched those previously reported for this compound.[52]



1-63 **1-64**

Ethyl 3-(tert-butyldimethylsilyloxy)-4-methylpent-3-enoate (1-64). 2-Bromo-2-methyl propionyl bromide (3.4 g, 15 mmol) was added dropwise to a suspension of activated zinc dust (1.9 g, 30 mmol) in THF (25 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then transferred via cannula to a solution of silyl ketene acetal **1-63** (1.0 g, 4.9 mmol) in THF

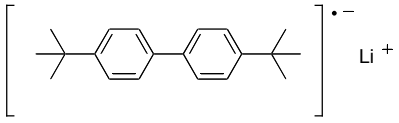
(25 mL) at 0 °C. The gray-green mixture was slowly warming to room temperature and stirred for 14 h. The reaction mixture was then diluted with Et_2O (25 mL) and washed with H_2O (15 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (5:1:94 Et_2O:Et_3N:hexanes) of the crude residue afforded ethyl ester **1-64** as a colorless oil (0.81 g, 60%): R_f = 0.40 (5% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, J = 7.1 Hz, 2H), 3.15 (s, 2H), 1.64 (s, 3H), 1.62 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 137.6, 113.7, 60.8, 38.9, 26.0, 19.3, 18.4, 18.2, 14.5, –3.9; IR (thin film) 2931, 2858, 1739, 1682, 1473, 1257 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{14}H_{28}O_3SiNa$ $[M + Na]^+$ 295.1705, found 295.1703.



3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,4-dimethylpent-3-enamide (1-61). A solution of *i*-PrMgCl (0.62 mL, 1.2 mmol, 2.0 M in Et_2O) was added dropwise to a solution of ethyl ester **1-64** (140. mg, 0.514 mmol) and Me(MeO)NH•HCl (60. mg, 0.62 mmol) in THF (50 mL) at –20 °C. The reaction mixture was stirred for 1 h at –20 °C, warmed to 0 °C, and the reaction was then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O (2 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography (30:1:69 Et_2O:Et_3N:hexanes) of the crude residue afforded Weinreb amide **1-61** as a colorless oil (122 mg, 83%): R_f = 0.28 (30% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.30 (s, 2H), 3.17 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (126 MHz,

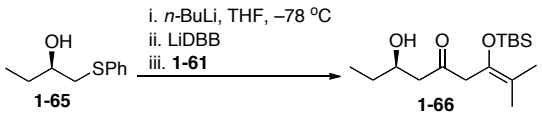
$CDCl_3$) δ 171.8, 137.9, 113.3, 61.3, 37.3, 32.5, 26.1, 19.3, 18.4, 18.3, –3.8; IR (thin film) 2931, 2858, 1678, 1462, 1254 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{14}H_{29}NO_3Si$ $[M + Na]^+$ 310.1814, found 310.1819.

(*R*)-1-(Phenylthio)butan-2-ol (1-65). A mixture of $LiClO_4$ (0.30 g, 2.8 mmol), (*R*)-1,2 epoxybutane (**1-35**, 2.0 mL, 23 mmol), and thiophenol (2.9 mL, 29 mmol) was stirred for 48 h. Purification by column chromatography (1:4 Et_2O:hexanes) of the crude residue produced *β*-thiophenyl alcohol **1-65** as a colorless oil (4.23 g, 98%): R_f = 0.30 (25% Et_2O/hexanes); $[\alpha]^{24}_D$ = –57.9 (*c* 1.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4, 2H), 7.30 (t, *J* = 7.9, 2H), 7.22 (t, *J* = 8.0, 1H), 3.63–3.58 (m, 1H), 3.16 (dd, *J* = 13.7, 3.4, 1H), 2.85 (dd, *J* = 13.7, 8.8, 1H), 2.38 (s, 1H), 1.62–1.53 (m, 2H), 0.97 (t, *J* = 7.5, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 130.3, 129.3, 126.8, 70.8, 42.1, 29.2, 10.2; IR (thin film) 3398, 3059, 2965, 2877, 1585, 1481, 1087 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{10}H_{14}OS$ $[M + Na]^+$ 205.0663, found 205.0662.



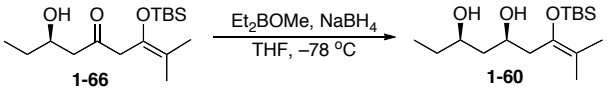
Lithium di-*tert*-butylbiphenylide. A two neck round-bottom flask equipped with a glass stir bar and 4,4'-di-*tert*-butylbiphenyl (0.99 g, 3.7 mmol) was heated with a torch *in vacuo* until sublimation occured. The flask was purged with argon and one crystal of 1,10-phenanthroline was added under positive argon pressure. Dry THF (7.4 mL) was added and the solution was cooled to 0 °C. The reaction mixture was titrated with *n*-butyllithium (2.2 M in hexanes) until a

dark red-brown color persisted to remove any trace H_2O. Lithium metal (180. mg, 26.0 mmol) was rinsed with hexanes and cut into the reaction flask. The solution turned dark green after 20 s and the reaction mixture was stirred for 5 h at 0 °C. The LiDBB (nominally 0.4 M) was used directly in the next reaction.



(*R*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-2-methylnon-2-en-5-one (1-66). To a two neck round-bottom flask equipped with a glass stir bar was added a crystal of indicator 1,10-phenanthroline, β-thiophenyl alcohol **1-65** (3.8 g, 21 mmol), and THF (41 mL). The reaction mixture was cooled to –78 °C and titrated with *n*-butyllithium (8.0 mL, 21 mmol, 2.6 M in hexanes) until a dark red-brown color persisted. A solution of nominally 0.4 M LiDBB (40 mmol) in THF was added portion wise to the reaction mixture until a green-blue color persisted for 10 min. When the reaction turned an orange-brown color, Weinreb amide **1-61** was added dropwise. The mixture was stirred for 22 h at –78 °C, then warmed to 0 °C, and the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The reaction mixture was extracted with Et_2O (4 x 100 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (10:9:1 hexanes:CH_2Cl_2:EtOAc) of the crude residue furnished ketone **1-66** as a clear yellow oil (1.71 g, 82%): R_f = 0.31 (10:9:1 hexanes: CH_2Cl_2:EtOAc); $[\alpha]^{24}_D$ = –29.9 (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01–3.88 (m, 1H), 3.19 (s, 2H), 3.05 (d, *J* = 2.9 Hz, 1H), 2.68 (dd, *J* = 17.7, 2.6 Hz, 1H), 2.53 (dd, *J* = 17.7, 9.2 Hz, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 1.61–1.38 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (126 MHz,

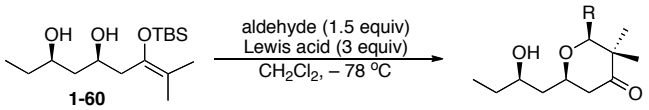
$CDCl_3$) δ 209.9, 137.7, 114.5, 69.3, 48.4, 47.0, 29.4, 26.0, 19.4, 18.3, 18.2, 10.0, –3.8; IR (thin film) 3444, 2962, 2862, 1712, 1678, 1462, 1254 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{16}H_{32}O_3SiNa$ $[M + Na]^+$ 323.2018, found 323.2010.



1-66 **1-60**

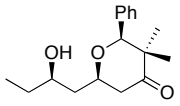
(3*R*,5*R*)-7-(*tert*-Butyldimethylsilyloxy)-8-methylnon-7-ene-3,5-diol (1-60). A solution of Et_2BOMe (0.92 mL, 0.92 mmol, 1.0 M in THF) was added dropwise to a solution of ketone **1-66** (250 mg, 0.83 mmol) in THF (13 mL) and MeOH (25 mL) at –78 °C. After 30 min, $NaBH_4$ (35 mg, 0.92 mmol) was added and the reaction mixture was stirred for 4 h at –78 °C. Acetic acid (0.53 mL, 9.3 mmol) was added dropwise and the solution was warmed to room temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL). The crude product was extracted with EtOAc (6 x 15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was diluted with methanol, stirred for 15 h at room temperature, and concentrated under reduced pressure in order to remove bound Et_2BOMe. The crude residue was diluted again with MeOH, stirred for another 2 h at room temperature, and concentrated to remove residual bound Et_2BOMe. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded diol **1-60** as a clear colorless oil (200 mg, 80%): R_f = 0.23 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = –4.2 (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dtd, *J* = 12.5, 4.6, 2.4 Hz, 1H), 3.82–3.75 (m, 1H), 3.44 (br. s, 1H), 2.89 (br. s, 1H), 2.35 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.24 (dd, *J* = 14.1, 4.6 Hz, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 1.60–1.56 (m, 1H), 1.54–1.45 (m, 3H), 0.95 (s, 9H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 113.5, 74.0, 72.0, 42.3, 40.5, 30.7, 26.0, 19.3, 18.4, 18.3, 9.8,

–3.69, –3.74; IR (thin film) 3356, 2931, 2858, 1678, 1462, 1257 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{16}H_{34}O_3SiNa$ $[M + Na]^+$ 325.2175, found 325.2176.



1-60

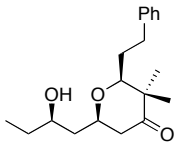
General Procedure for the Silyl Enol Ether Prins Cyclization: Lewis acid (0.90 mmol) was added dropwise to a solution of diol **1-60** (0.30 mmol), 0.75 mL CH_2Cl_2, and aldehyde (0.45 mmol) at –78 °C. The reaction mixture was stirred for 4 h at –78 °C; the mixture was removed from the –78 °C bath and the reaction was immediately quenched with saturated aqueous $NaHCO_3$. The solution was extracted with CH_2Cl_2 (3 x 2 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography of the crude residue afforded desired THPO.



1-67a

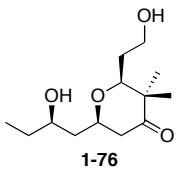
(2*S*,6*R*)-6-((*R*)-2-hydroxybutyl)-3,3-dimethyl-2-phenyldihydro-2H-pyran-4(3H)-one (1-67a). Alcohol **1-60** (93 mg, 0.31 mmol) and benzaldehyde (53 mg, 0.50 mmol) were converted to **1-67**a following the general procedure for the silyl enol ether Prins cyclization. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded THPO **1-67**a as a yellow oil (55 mg, 64%): R_f = 0.28 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = 38.6 (*c* 0.86, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 5H), 4.42 (s, 1H), 4.06–4.01 (m, 1H), 3.79–3.75 (m, 1H), 3.42 (s, 1H), 2.78 (dd, *J* = 14.4, 12.0 Hz, 1H), 2.40 (dd, *J* = 14.4, 2.6 Hz, 1H), 1.89 (app. dt, *J* = 14.6, 9.8 Hz, 1H), 1.73 (dt, *J* = 14.6, 2.0 Hz, 1H), 1.57–1.44 (m, 2H), 1.04 (s, 3H), 0.96 (s,

3H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.7, 136.6, 128.2, 128.0, 127.7, 86.4, 79.0, 72.9, 50.5, 44.8, 42.9, 30.4, 19.8, 19.4, 9.9; IR (neat) 3491, 2970, 2935, 2877, 1712 cm^{-1}; HRMS (ES/MeOH) m / z calc for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1630.



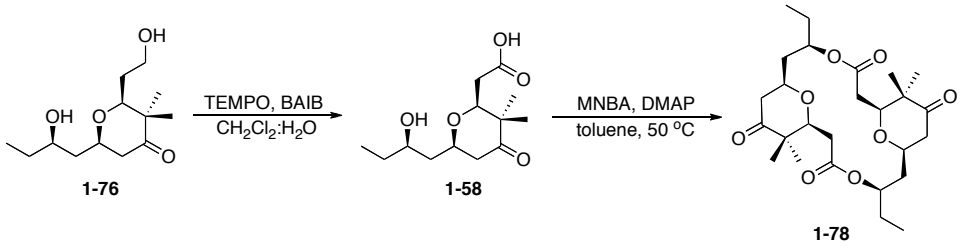
1-67b

(2*S*,6*R*)-6-((*R*)-2-hydroxybutyl)-3,3-dimethyl-2-phenethyldihydro-2*H*-pyran-4(3*H*)-one (1-67b). Diol **1-60** (50 mg, 0.16 mmol) and dihydrocinnamaldehyde (33 mg, 0.24 mmol) were converted to **1-67**b following the general procedure for the silyl enol ether Prins cyclization. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded THPO **1-67**b as a yellow oil (28 mg, 56%): R_f = 0.50 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = –96.5 (*c* 0.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.21–7.18 (m, 3H), 3.86–3.80 (m, 2H), 3.35 (s, 1H), 3.27 (d, J = 9.9 Hz, 1H), 2.92–2.87 (m, 1H), 2.65–2.56 (m, 2H), 2.28 (dd, J = 14.3, 2.4 Hz, 1H), 1.93–1.85 (m, 1H), 1.85–1.73 (m, 2H), 1.69–1.66 (m, 2H), 1.59–1.51 (m, 1H), 1.11 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9, 141.4, 128.7, 128.6, 126.2, 83.7, 78.4, 72.8, 49.5, 45.0, 42.7, 33.0, 31.1, 30.3, 19.4, 18.9, 9.8; IR (neat) 3491, 2966, 2931, 2873, 2858, 1712 cm^{-1}; HRMS (ES/MeOH) m / z calc for $C_{19}H_{28}O_3Na$ $[M + Na]^+$ 327.1936, found 327.1940.



1-76

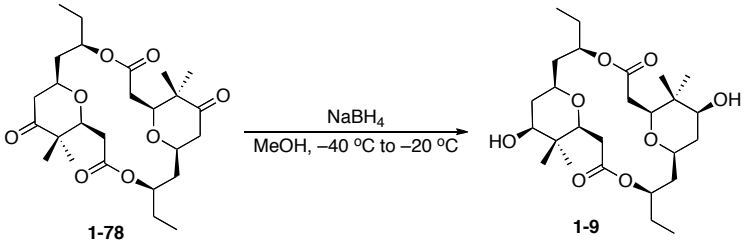
(2*S*,6*R*)-6-((*R*)-2-hydroxybutyl)-2-(2-hydroxyethyl)-3,3-dimethyldihydro-2H-pyran-4(3H)-one (1-76). Diol **1-60** (100 mg, 0.32 mmol) and aldehyde **1-59**[53] (R=TBS, 190 mg, 1.0 mmol) were converted to **1-76** following the general procedure for the silyl enol ether Prins cyclization. Three equiv of the aldehyde was used instead of 1.5 equiv from the general procedure. Purification by column chromatography (7:3 EtOAc:hexanes) of the crude residue afforded THPO **1-76** as a yellow oil (44 mg, 56%): R_f = 0.30 (70% EtOAc/hexanes); $[\alpha]^{24}_D$ = –77.9 (*c* 1.95, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90–3.84 (m, 1H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.79–3.74 (m, 1H), 3.53 (dd, *J* = 10.4, 1.7 Hz, 1H), 2.59 (dd, *J* = 14.3, 12.2 Hz, 1H), 2.30 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.89–1.82 (m, 2H), 1.80–1.76 (m, 1H), 1.73–1.68 (m, 1H), 1.62 (dt, *J* = 14.7, 2.6 Hz, 1H), 1.56– 1.47 (m, 2H), 1.14 (s, 3H), 1.01 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.8, 83.6, 78.2, 72.7, 61.2, 49.3, 45.0, 42.7, 31.6, 30.7, 19.5, 18.9, 9.8; IR (neat) 3456, 2966, 2935, 2877, 1709 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{13}H_{24}O_4Na$ $[M + Na]^+$ 267.1572, found 267.1580.



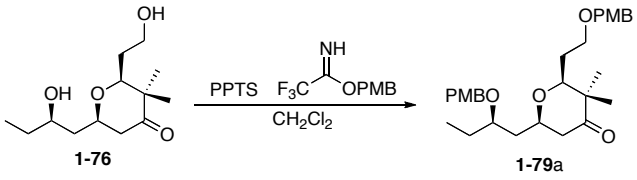
1-76 **1-58** **1-78**

Macrocycle 1-78. [Bis(acetoxy)iodo]benzene (22 mg, 0.69 mmol) was added to a vial containing THPO **1-76** (14 mg, 34 μmol), CH_2Cl_2 (0.34 mL), and H_2O (0.34 mL). 2,2,6,6-Tetramethyl-1-piperidinyloxyl, TEMPO, (5.3 mg, 34 μmol) dissolved in 0.1 mL CH_2Cl_2

was added to the reaction mixture. The solution was stirred vigorously under argon for 3 h with additional TEMPO added after 1 h and 2.5 h, 5.3 mg (34 μmol) in 0.1 mL CH_2Cl_2 and 2.7 mg (17 μmol) in 0.05 mL CH_2Cl_2, relatively. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and the solution was extracted with CH_2Cl_2 (4 x 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to obtain THPO **1-58** as a red oil, which was employed in the next step without further purification. Carboxylic acid **1-58** in toluene (61 mL) was added slowly to a solution of 2-methyl-6-nitrobenzoic anhydride (190 mg, 0.55 mmol) and DMAP (0.45 g, 3.7 mmol) in toluene (46 mL), via syringe pump at 50 ºC over 24 h. The mixture was stirred for an additional 30 min and then concentrated *in vacuo*. The residue was purified by column chromatography (1:3 EtOAc:hexanes) to afford macrocycle **1-78** as a colorless oil (4.4 mg, 10%): R_f = 0.21 (25% EtOAc/hexanes); $[\alpha]^{24}_D = -119.0$ (*c* 1.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (dd, *J* = 6.9, 6.4 Hz, 2H), 3.85–3.77 (m, 4H), 2.50–2.40 (m, 6H), 2.35 (td, *J* = 13.3, 2.1 Hz, 2H), 1.89 (ddd, *J* = 15.2, 9.8, 7.7 Hz, 2H), 1.65–1.54 (m, 6H), 1.10 (s, 6H), 1.00 (s, 6H), 0.87 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6, 170.2, 79.9, 77.0, 74.2, 48.8, 44.9, 40.2, 35.0, 28.4, 19.6, 19.0, 9.3; IR (thin film) 2970, 2877, 1739, 1712, 1466, 1385, 1304, 1196 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{26}H_{40}O_8Na$ $[M + Na]^+$ 503.2621, found 503. 2614. Characterization matches those previously reported for this compound.[8]

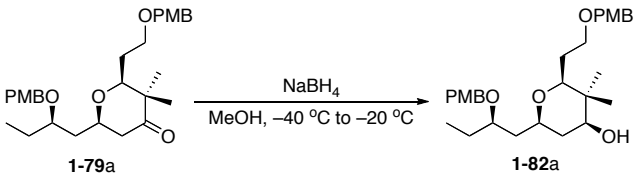


Cyanolide A aglycone (1-9). A solution of diketone **1-78** (24.6 mg, 0.0512 mmol) in 1.5 mL of MeOH was cooled to –40 °C and $NaBH_4$ (4.1 mg, 0.107 mmol) was added. The mixture was allowed to warm to –20 °C over 2 h and then saturated aqueous NH_4Cl was added. The mixture was extracted with Et_2O (2 × 10 mL) and the combined organic fractions were dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification of the crude residue by column chromatography (3:2 EtOAc:hexanes) afforded the title compound as a white film (23.8 mg, 96%): R_f = 0.23 (60% EtOAc/hexanes); $[\alpha]^{24}_D$ = –36.6 (*c* 0.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (dd, *J* = 14.6, 6.7 Hz, 2H), 3.46 (dd, *J* = 11.6, 4.9 Hz, 4H), 3.39 (d, *J* = 7.9 Hz, 2H), 2.40 (dd, *J* = 15.7, 1.1 Hz, 2H), 2.28 (dd, *J* = 15.8, 9.1 Hz, 2H), 1.91–1.81 (m, 4H), 1.65–1.50 (m, 8H), 1.33 (q, *J* = 11.8 Hz, 2H), 0.93 (s, 6H), 0.87 (t, *J* = 7.4 Hz, 6H), 0.83 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 80.8, 75.4, 75.1, 73.8, 41.1, 38.8, 37.3, 35.4, 28.3, 22.4, 12.6, 9.7; IR (thin film) 3440, 2970, 2881, 1732, 1469, 1373, 1304, 1203 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{26}H_{44}O_8Na$ $[M + Na]^+$ 507.2934, found 507.2922. Characterization matches those previously reported for this compound.[8]



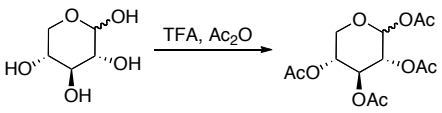
(2*S*,6*R*)-6-((*R*)-2-(4-methoxybenzyloxy)butyl)-2-(2-(4-methoxybenzyloxy)ethyl)-3,3-dimethyldihydro-2H-pyran-4(3H)-one (1-79a). Pyridinium *p*-toluenesulfonate (30 mg,

0.12 mmol) was added to a vial containing diol **1-76** (62 mg, 0.25 mmol). The mixture was diluted with PMB acetimidate (244 mg, 1.05 mmol) in 0.85 mL CH_2Cl_2 and stirred for 24 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the mixture was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic fractions were dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:3 EtOAc:hexanes) of the crude residue afforded ketone **1-79**a as a clear colorless oil (56 mg, 45%) along with the mono-PMB ether (27 mg, 31%). The mono-PMB protected product was resubjected to the protection conditions to deliver additional ketone **1-79**a. **For ketone 1-79a**: R_f = 0.52 (25% EtOAc/hexanes); $[\alpha]^{24}_D$ = –48.0 (*c* 0.23, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (app. t, *J* = 7.0 Hz, 4H), 6.87 (app. dd, *J* = 7.1, 2.6 Hz, 4H), 4.47–4.37 (m, 4H), 3.80 (s, 3H), 3.79 (s, 3H), 3.70–3.65 (m, 1H), 3.60–3.56 (m, 1H), 3.53 (t, *J* = 6.4 Hz, 1H), 3.46 (quintet, *J* = 4.9 Hz, 1H), 3.38 (dd, *J* = 6.3, 4.0 Hz, 1H), 2.47 (dd, *J* = 11.6, 9.5 Hz, 1H), 2.23 (dd, *J* = 12.9, 2.0 Hz, 1H), 1.99 (dt, *J* = 11.4, 5.9 Hz, 1H), 1.78–1.75 (m, 2H), 1.63–1.52 (m, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 0.91 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.9, 159.3 (2), 130.9, 130.6, 129.6, 129.5, 129.3, 114.6, 114.0, 113.9, 80.8, 76.2, 74.6, 72.9, 70.5, 67.3, 55.4, 49.2, 44.8, 40.2, 26.2, 19.4, 19.0, 9.4; IR (thin film) 2963, 2934, 2863, 1709, 1612, 1585, 1513, 1248 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{29}H_{40}O_6Na$ $[M + Na]^+$ 507.2722, found 507.2711.



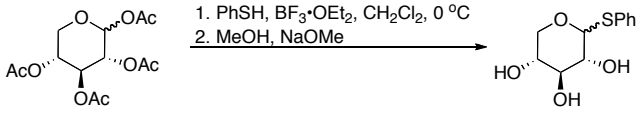
1-79a **1-82**a

(2*S*,4*S*,6*S*)-6-((*R*)-2-(4-methoxybenzyloxy)butyl)-2-(2-(4-methoxybenzyloxy)ethyl)-3,3-dimethyltetrahydro-2H-pyran-4-ol (1-82a). To a vial containing ketone **1-79**a (54 mg, 0.11 mmol) was added MeOH (0.56 mL). The mixture was cooled to –40 ºC and $NaBH_4$ (4.6 mg, 0.12 mmol) was added. The reaction mixture was stirred for 1 h, slowly warming to –20 ºC, and then saturated aqueous NH_4Cl (2 mL) was added. The solution was extracted with EtOAc (4 x 5 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (2:3 EtOAc:hexanes) of the crude residue afforded the title compound as a clear colorless oil (44 mg, 82%): R_f = 0.39 (40% EtOAc/hexanes); $[\alpha]^{24}_D$ = –35.5 (*c* 0.47, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (app. t, *J* = 7.9 Hz, 4H), 6.87 (dd, *J* = 8.6, 1.6 Hz, 4H), 4.58–4.36 (m, 4H), 3.80 (s, 3H), 3.79 (s, 3H), 3.54–3.43 (m, 4H), 3.36 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.05 (dd, *J* = 10.5, 1.2 Hz, 1H), 1.89 (app. quintet, *J* = 6.8 Hz, 1H), 1.81–1.76 (m, 1H), 1.63–1.48 (m, 6 H) 1.31 (app. q, *J* = 11.8 Hz, 1H), 0.91 (s, 3H), 0.90 (t, *J* = 7.7 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.24, 159.23, 131.2, 130.8, 129.6, 129.4, 113.90, 113.88, 80.5, 76.5, 76.1, 73.1, 72.8, 70.4, 67.9, 55.44, 55.40, 39.8, 38.9, 37.2, 29.5, 26.2, 22.5, 12.6, 9.6. IR (thin film) 3458, 2960, 2932, 2855, 1613, 1514, 1464 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{29}H_{42}O_6Na$ $[M + Na]^+$ 509.2879, found 509.2866.



1-57 **1-83**

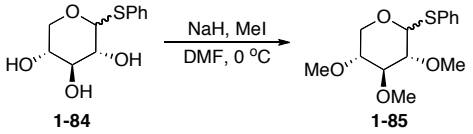
Tetra-*O*-acetyl-D-xylopyranose (1-83). Trifluoroacetic acid (6.4 mL, 83 mmol) was added to a suspension of D-(+)-xylose (**1-57**, 10.0 g, 66.6 mmol) in acetic anhydride (128 mL). The reaction mixture was stirred at room temperature for 3 h until all the solid had been consumed. The mixture was concentrated, diluted with toluene, and concentrated again *in vacuo* (3 x 25 mL) to form a thick yellow oil, which was dissolved in methanol and washed with hexanes (3 x 25 mL). The solvent was removed *in vacuo*. Purification by column chromatography (1:1 EtOAc:hexanes) of the crude residue produced tetra-*O*-acetyl-D-xylopyranose **1-83** as a viscous yellow liquid (18.6 g, 88%). ^{1}H and ^{13}C NMR spectra matched those previously reported for this compound.[44]



1-83 **1-84**

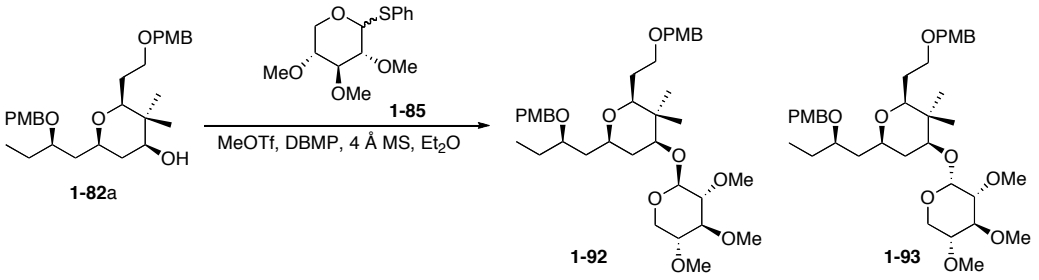
(3*R*,4*S*,5*R*)-2-(phenylthio)tetrahydro-2*H*-pyran-3,4,5-triol (1-84). Thiophenol (1.2 ml, 11 mmol) and BF_3•Et_2O (3.4 ml, 27.05 mmol) were added to a solution of **1-83** (2.9 g, 9.0 mmol) in CH_2Cl_2 (11.5 mL) at 0 °C. The reaction mixture was stirred for 6 h at room temperature, then diluted with CH_2Cl_2 (10 mL) and the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The resulting solution was washed successively with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (2 x 10 mL). Washes were back-extracted with CH_2Cl_2 (1 x 15 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in methanol (9 mL) and a solution of sodium methoxide (300 mL, 30. mmol,

0.1 M in methanol) was added. After 20 min, the mixture was neutralized with activated Amberlite IR=120(H^+) resin, filtered, and concentrated. After recrystallization of the residue from acetone-hexanes, triol **1-84** was obtained as a light yellow solid (1.24 g, 57%). ^{1}H and ^{13}C NMR spectra matched those previously reported for this compound.[45]



1-84 **1-85**

(3*R*,4*S*,5*R*)-3,4,5-trimethoxy-2-(phenylthio)tetrahydro-2*H*-pyran (1-85). Sodium hydride (400. mg, 16.5 mmol) was added to a solution of thioether **1-84** (1.0 g, 4.1 mmol) in DMF (21 mL) at 0 °C. The suspension was stirred for 50 min at 0 °C and then MeI (1.5 mL, 25 mmol) was added dropwise. The mixture was stirred for an additional 4.5 h at 0 °C and the reaction was quenched with H_2O (50 mL). The solution was extracted with EtOAc (4 x 50 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (1:4 EtOAc:hexanes) to afford thioether **1-85** as a light yellow oil (0.43 g, 36%). ^{1}H and ^{13}C NMR spectra matched those previously reported for this compound.[44]

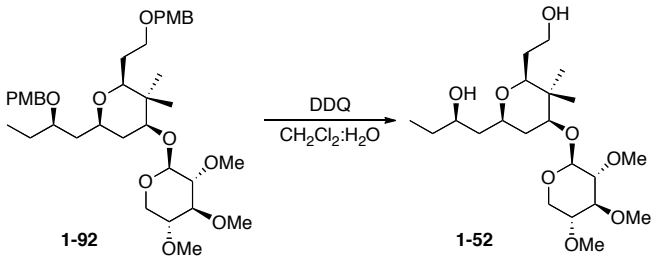


1-82a **1-92** **1-93**

(2*S*,4*S*,6*R*)-6-((*R*)-2-(4-methoxybenzyloxy)butyl)-2-(2-(4-methoxybenzyloxy)ethyl)-3,3-dimethyl-4-((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2*H*-pyran-2-yloxy)tetrahydro-2*H*-

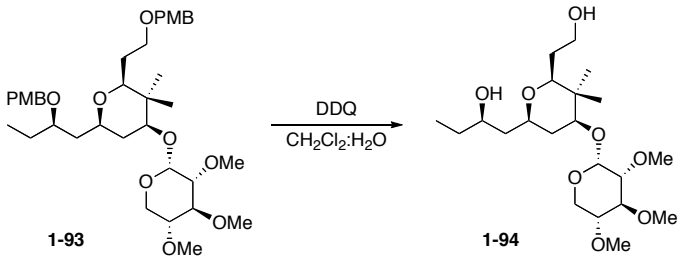
pyran (1-92) and (2*S*,4*S*,6*R*)-6-((*R*)-2-(4-methoxybenzyloxy)butyl)-2-(2-(4-methoxybenzyloxy)ethyl)-3,3-dimethyl-4-((2*R*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2*H*-pyran-2-yloxy)tetrahydro-2*H*-pyran (1-93). In a glovebox, alcohol **1-82**a (136 mg, 0.28 mmol), thioether **1-85** (119 mg, 0.42 mmol), and Et_2O (4 mL) was added to a vial containing 4 Å molecular sieves (122 mg, 200 wt% of alcohol) and DBMP (115 mg, 0.56 mmol). The mixture was stirred for 20 min at room temperature and MeOTf (62 μL, 0.56 mmol) was added. After stirring for 96 h at 25 ºC in a sealed vial, the reaction was quenched with saturated $NaHCO_3$ in anhydrous *i*-PrOH (10 mL). The solution was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (3:7 EtOAc:hexanes) followed by preparatory HPLC (3:7 EtOAc:hexanes) to afford glycoside **1-92** (73 mg, 42%) along with the α-anomer **1-93** (23 mg, 12%), both as clear colorless oils. **For glycoside 1-92**: R_f = 0.40 (30% EtOAc/hexanes); $[\alpha]^{24}_D$ = –44.8 (*c* 0.82, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 9.9, 8.8 Hz, 4H), 6.86 (app. d, *J* = 8.3 Hz, 4H), 4.44–4.37 (m, 4H), 4.23 (d, *J* = 7.6 Hz, 1H), 3.94 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.62 (s, 3H), 3.61 (s, 3H), 3.46 (s, 3H), 3.56–3.40 (m, 4H), 3.27–3.21 (m, 2H), 3.11–3.04 (m, 3H), 2.97 (dd, *J* = 9.0, 7.7 Hz, 1H), 1.92–1.84 (m, 2H), 1.82–1.76 (m, 1H), 1.64–1.53 (m, 2H), 1.52–1.47 (m, 3H), 0.95 (s, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 159.21, 159.17, 131.3, 130.8, 129.4, 129.3, 113.88, 113.86, 106.1, 86.1, 85.7, 84.2, 80.6, 79.5, 76.9, 73.1, 72.8, 70.5, 67.8, 63.4, 61.1, 61.0, 59.0, 55.40, 55.38, 39.8, 39.0, 36.9, 29.4, 26.2, 22.3, 13.6, 9.5; IR (neat) 2934, 2836, 1612, 1586 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{37}H_{56}O_{10}Na$ $[M + Na]^+$ 683.3771, found 683.3784. **For α-anomer 1-93**: R_f = 0.33 (30% EtOAc/hexanes); $[\alpha]^{24}_D$ = 21.7 (*c* 0.15, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.2, 4.2 Hz, 4H), 6.87 (dd, *J* = 8.7, 2.3 Hz,

4H), 4.87 (d, *J* = 3.4 Hz, 1H), 4.46–4.37 (m, 4H), 3.791 (s, 3H), 3.790 (s, 3H), 3.68 (dd, *J* = 3.7 Hz, 1H), 3.62 (s, 3H), 3.57–3.53 (m, 2H), 3.51–3.38 (m, 4H), 3.48 (s, 3H), 3.39 (s, 3H), 3.32 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.26–3.21 (m, 1H), 3.11 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.07 (dd, *J* = 11.0, 1.2 Hz, 1H), 1.92 (ddd, *J* = 14.2, 7.1, 6.5 Hz, 1H), 1.70–1.66 (m, 1H), 1.64–1.49 (m, 4H), 1.33–1.24 (m, 2H), 0.96 (s, 3H), 0.90 (t, *J* = 7.7 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 159.23, 159.22, 131.2, 130.9, 129.6, 129.3, 113.89, 113.86, 92.9, 82.3, 81.6, 80.7, 80.1 (2), 77.4, 76.1, 72.8, 70.1, 67.8, 61.0, 60.1, 59.1, 58.4, 55.4 (2), 39.9, 38.4, 32.7, 29.4, 26.0, 23.3, 13.7, 9.5; IR (neat) 2933, 1612, 1586 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{37}H_{56}O_{10}Na$ $[M + Na]^+$ 683.3771, found 683.3757.



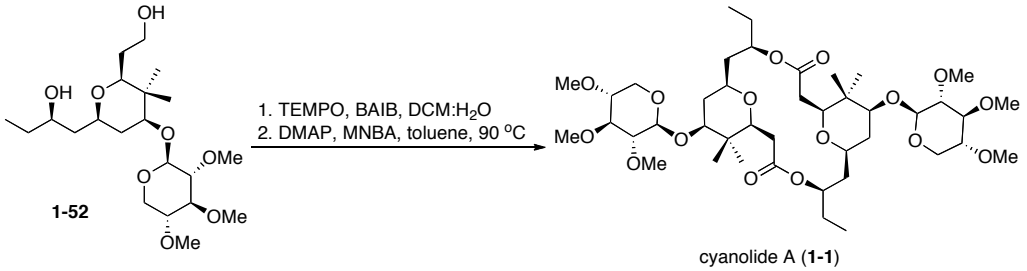
(*R*)-1-((2*R*,4*S*,6*S*)-6-(2-hydroxyethyl)-5,5-dimethyl-4-((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yloxy)tetrahydro-2H-pyran-2-yl)butan-2-ol (1-52a). To a vial containing **1-92** (28 mg, 42 μmol) and CH_2Cl_2:H_2O (18:1 ratio, 1.4 mL) was added DDQ (24 mg, 0.10 mmol). The reaction mixture was capped and stirred at room temperature for 3 h, turning from a spinach green to an orange color. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 mL), and the mixture was diluted with CH_2Cl_2 (5 mL), and stirred for 10 min. The solution was extracted with CH_2Cl_2 (7 x 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (100% EtOAc) of the crude residue afforded the title compound as a white film

(15 mg, 83%): R_f = 0.50 (100% EtOAc); $[\alpha]^{24}_D$ = –47.5 (*c* 1.67, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (d, *J* = 7.6 Hz, 1H), 3.93 (dd, *J* = 5.2, 11.6 Hz, 1H), 3.76–3.67 (m, 3H), 3.63–3.59 (m, 1H), 3.600 (s, 3H), 3.596 (s, 3H), 3.45 (s, 3H), 3.26 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.22–3.20 (m, 2H), 3.09–3.04 (m, 2H), 2.96 (app. t, *J* = 7.8 Hz, 1H), 1.89–1.86 (m, 1H), 1.73–1.53 (m, 5H), 1.49–1.39 (m, 2H), 1.00 (s, 3H), 0.900 (t, *J* = 7.4 Hz, 3H), 0.896 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 106.2, 85.7, 85.4, 84.1, 83.0, 79.5, 76.9, 73.1, 63.4, 61.14, 61.10, 61.0, 59.0, 42.1, 39.0, 37.0, 31.2, 30.6, 22.2, 13.6, 9.9; IR (thin film) 3434, 2934, 1463 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{21}H_{40}O_8Na$ $[M + Na]^+$ 443.2621, found 443.2615.



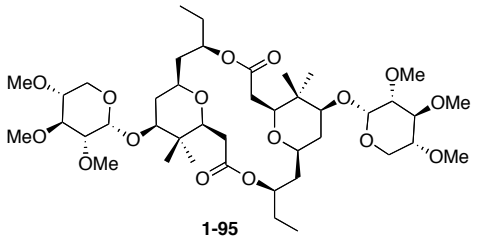
(*R*)-1-((2*R*,4*S*,6*S*)-6-(2-hydroxyethyl)-5,5-dimethyl-4-((2*R*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2*H*-pyran-2-yloxy)tetrahydro-2*H*-pyran-2-yl)butan-2-ol (1-94). To a vial containing **1-93** (23 mg, 0.035 mmol) and CH_2Cl_2:H_2O (18:1 ratio, 1.2 mL) was added DDQ (20 mg, 0.088 mmol). The reaction mixture was capped and stirred at room temperature for 3 h, turning from a spinach green to an orange color. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 mL), diluted with CH_2Cl_2 (5 mL), and stirred for 10 minutes. The mixture was extracted with CH_2Cl_2 (4 x 5 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (100% EtOAc) of the crude residue afforded the title compound as a white film (10 mg, 65%): R_f = 0.21 (100% EtOAc); $[\alpha]^{24}_D$ = 45.8 (*c* 0.48, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 3.6, 1H), 3.76 – 3.72

(m, 3H), 3.68 (dd, J = 8.5, 4.8, 1H), 3.62–3.57 (m, 1H), 3.62 (s, 3H), 3.53 (app. t, J = 10.9, 1H), 3.48 (s, 3H), 3.45 (s, 3H), 3.43–3.36 (m, 3H), 3.26–3.21 (m, 2H), 3.14 (dd, J = 3.6, 9.5, 1H), 1.83–1.80 (m, 1H), 1.74–1.64 (m, 3H), 1.59–1.56 (m, 1H), 1.49–1.40 (m, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.92 (t, J = 7.3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 93.1, 83.2, 82.3, 81.5, 80.0, 79.5, 76.8, 73.1, 61.3, 61.0, 60.2, 59.1, 58.6, 42.4, 38.5, 33.0, 31.3, 30.7, 23.3, 13.6, 9.9; IR (thin film) 3437, 2932, 1464 cm^{-1}; HRMS (ES/MeOH) m/z calc for $C_{21}H_{40}O_8Na$ $[M + Na]^+$ 443.2621, found 443.2601.



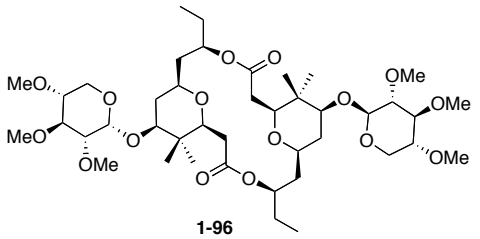
Cyanolide A (1-1). [Bis(acetoxy)iodo]benzene, BIAB, (31 mg, 96 mmol) was added to a vial containing THP **1-52** (20 mg, 48 mmol), CH_2Cl_2 (0.48 mL), and H_2O (0.48 mL). 2,2,6,6-Tetramethyl-1-piperidinyloxy, TEMPO, (7.6 mg, 48 mmol) dissolved in 0.2 mL CH_2Cl_2 was added to the reaction mixture. The mixture was stirred vigorously under argon for 3 h with addition of TEMPO after 1 h and 2 h, 7.6 mg (48 mmol) in 0.2 mL CH_2Cl_2 and 3.8 mg (24 mmol) in 0.1 mL CH_2Cl_2, relatively. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and extracted with CH_2Cl_2 (4 x 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to obtain a carboxylic acid, which was employed in the next step without further purification. The carboxylic acid was diluted in toluene (16 mL) and added slowly to a solution of 2-methyl-6-nitrobenzoic anhydride, MNBA, (50 mg, 0.14 mmol) and DMAP (117 mg, 0.96 mmol) in toluene (12 mL), via syringe pump at 90 °C over

5 h. The reaction mixture stirred for an additional 30 min and was then concentrated *in vacuo*. The residue was purified by column chromatography (7:3 EtOAc:Hex) to afford cyanolide A (**1-1**) as a colorless oil (18 mg, 88%): R_f = 0.63 (70% EtOAc/hexanes); $[\alpha]^{24}_D$ = –48.3 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (app. q, *J* = 7.1 Hz, 2H), 4.26 (d, *J* = 7.7 Hz, 2H), 3.98 (dd, *J* = 11.7, 5.3 Hz, 2H), 3.63 (s, 6H), 3.62 (s, 6H), 3.47 (s, 6H), 3.45 (m, 4H), 3.44–3.40 (m, 4H), 3.32 (dd, *J* = 11.7, 5.3 Hz, 2H), 3.27–3.22 (m, 2H), 3.07–3.01 (m, 4H), 2.98 (app. t, *J* = 7.7 Hz, 2H), 2.39 (dd, *J* = 16.2, 1.9 Hz, 2H), 2.28 (dd, *J* = 17.0, 9.0 Hz, 2H), 1.98–1.94 (m, 2H), 1.83 (dt, *J* = 15.7, 7.9 Hz, 2H), 1.62–1.45 (m, 8H), 0.97 (s, 6H), 0.89 (s, 6H), 0.86 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 106.1, 85.7, 85.5, 84.2, 80.5, 79.5, 75.4, 74.0, 63.4, 61.1, 61.0, 58.9, 40.8, 38.8, 37.1, 35.2, 28.4, 22.3, 13.7, 9.6; HRMS (ES/MeOH) *m* / *z* calcd for $C_{42}H_{72}O_{16}Na$ $[M + Na]^+$ 855.4718, found 855.4698. Characterization matches those previously reported for this compound.[8]



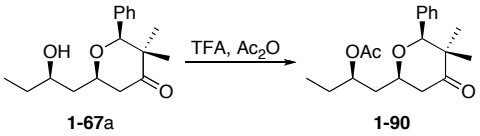
1-95

Macrocycle 1-95. Following the same procedure as (**1-1**) starting with glycoside **1-94** (5 mg, 12 μmol) afforded **1-95** as a colorless oil (1.5 mg, 30%). ^{1}H and ^{13}C NMR spectra matched those previously reported for this compound.[8]



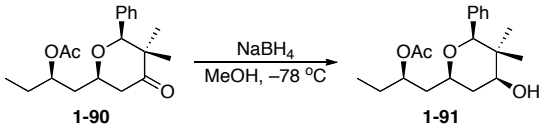
1-96

Macrocycle 1-96. Following the same procedure as (**1-1**) starting with a 1:1 mixture of glycoside **1-52** (3 mg, 7 μmol) and **1-95** (3 mg, 7 μmol) afforded a mixture of macrocycles **1-1**, **1-95**, and **1-96**. Macrocycle **1-96** was isolated as a colorless oil (2 mg, 30%). ^{1}H and ^{13}C NMR spectra matched those previously reported for this compound.[8]



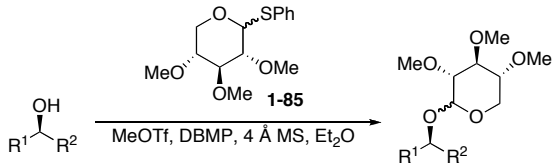
1-67a **1-90**

(*R*)-1-((2*R*,6*S*)-5,5-dimethyl-4-oxo-6-phenyltetrahydro-2*H*-pyran-2-yl)butan-2-yl acetate (1-90). A solution of THPO **1-67**a (43 mg, 0.15 mmol), trifluoroacetic acid (13 μL, 0.17 mmol), and acetic anhydride (0.4 mL) was stirred for 5 h at room temperature. The mixture was concentrated *in vacuo*. Purification by column chromatography (1:4 EtOAc:hexanes) of the resulting crude residue afforded ketone **1-90** as a light yellow oil (38 mg, 77%): R_f = 0.47 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 5H), 5.01–4.94 (m, 1H), 4.23 (s, 1H), 3.84–3.82 (m, 1H), 2.63 (dd, *J* = 14.1, 12.1 Hz, 1H), 2.33 (dd, *J* = 14.2, 2.6 Hz, 1H), 2.06–1.98 (m, 2H), 1.71 (s, 3H), 1.55–1.50 (m, 2H), 0.95 (s, 3H), 0.87 (s, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3, 170.9, 137.2, 128.1, 127.9, 127.7, 86.1, 75.4, 72.6, 50.3, 44.6, 40.3, 27.4, 21.1, 19.9, 19.4, 9.6; IR (neat) 2974, 2935, 2877, 1732, 1712 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{19}H_{26}O_4Na$ $[M + Na]^+$ 341.1729, found 341.1729.



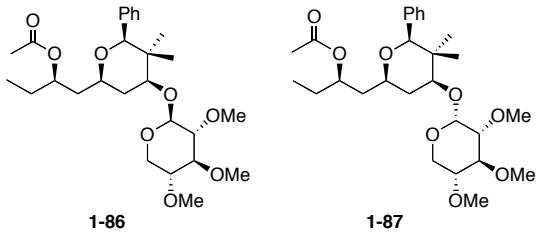
1-90 **1-91**

(*R*)-1-((2*S*,4*S*,6*S*)-4-hydroxy-5,5-dimethyl-6-phenyltetrahydro-2*H*-pyran-2-yl)butan-2-yl acetate (1-91). Sodium borohydride (2.4 mg, 0.060 mmol) was added to a solution of ketone **1-90** (18 mg, 0.060 mmol) in THF (0.58 mL) and methanol (0.13 mL) at –78 °C. The reaction mixture was stirred for 8 h and then 0.04 mL glacial acetic acid was added while warming to room temperature. Saturated aqueous $NaHCO_3$ was added to the mixture and the biphasic solution was extracted with EtOAc (4 x 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (3:7 EtOAc:hexanes) of the crude residue afforded alcohol **1-91** as a yellow oil (15 mg, 80%): R_f = 0.43 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 5H), 5.05–4.97 (m, 1H), 4.00 (s, 1H), 3.63–3.59 (m, 2H), 2.01–1.95 (m, 1H), 1.86 (m, 1H), 1.82 (s, 3H), 1.73–1.69 (dq, *J* = 12.5, 2.3 Hz, 2H), 1.60–1.52 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.85 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.6, 138.6, 128.2, 127.4, 127.3, 86.2, 76.1, 74.1, 72.9, 40.2, 39.9, 37.0, 27.6, 23.0, 21.2, 12.6, 9.7; IR (neat) 3464, 2974, 2935, 2877, 2858, 1732 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{19}H_{28}O_4Na$ $[M + Na]^+$ 343.1885, found 343.1884.



General Procedure for Glycosylation with Thioether 1-85. In a glovebox, alcohol (1.0 equiv), thioether **1-85** (1.5 equiv relative to -OH), and Et_2O (0.07 M) was added to a vial containing

4 Å molecular sieves (200 wt% of alcohol) and DBMP (2.0 equiv relative to -OH). The mixture was stirred for 20 min at room temperature and MeOTf (2.0 equiv relative to -OH) was added. After stirring for 48 h at 25 ^{o}C in a sealed vial, the reaction was quenched with saturated aqueous $NaHCO_3$. The solution was extracted four times with Et_2O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by preparative TLC or column chromatography to afford desired glycosylated product. Yields were not recorded, less than one milligram of material was necessary for biological testing.

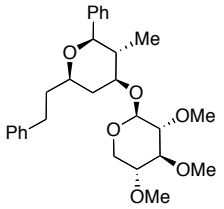


1-86

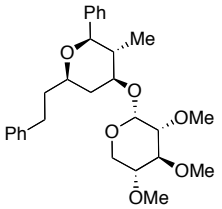
1-87

(*R*)-1-((2*R*,4*S*,6*S*)-5,5-dimethyl-6-phenyl-4-((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2*H*-pyran-2-yloxy)tetrahydro-2*H*-pyran-2-yl)butan-2-yl acetate (1-86) and (*R*)-1-((2*R*,4*S*,6*S*)-5,5-dimethyl-6-phenyl-4-((2*R*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yloxy)tetrahydro-2H-pyran-2-yl)butan-2-yl acetate (1-87). Following the general procedure for glycosylation with thioether **1-85**, THP **1-91** was transformed to THP **1-86** and **1-87**. **For THP 1-86**: Colorless oil; $R_f = 0.16$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 5H), 5.02–4.97 (m, 1H), 4.28 (d, J = 7.6 Hz, 1H), 4.01–3.97 (m, 2H), 3.62 (s, 3H), 3.57 (s, 3H), 3.47 (s, 3H), 3.44–345 (m, 1H), 3.28–3.23 (m, 1H), 3.13–3.08 (m, 2H), 2.98 (app. t, J = 7.9 Hz, 1H), 2.00–1.91 (m, 2H), 1.78 (s, 3H), 1.71–1.62 (m, 3H), 1.38–1.20 (m, 1H) 0.88 (s, 3H), 0.85 (t, J = 7.4 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 138.6, 128.3, 127.4, 127.3, 106.0, 86.3, 86.0, 85.7, 84.1, 79.6, 74.2, 73.1, 63.4, 61.1, 61.0, 59.0, 40.1,

40.0, 36.7, 27.5, 22.9, 21.2, 13.7, 9.7; IR (neat) 2966, 2931, 1732 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{27}H_{42}O_8Na$ $[M + Na]^+$ 517.2777, found 517.2776. **For THP 1-87**: Colorless oil; R_f = 0.12 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 5H), 5.03–4.97 (m, 1H), 5.01 (d, *J* = 3.4 Hz, 1H), 4.00 (s, 1H), 3.70 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.61 (s, 3H), 3.61–3.48 (m, 8H), 3.40 (t, *J* = 9.2 Hz, 1H), 3.27–3.22 (m, 2H), 3.16 (dd, *J* = 9.6, 3.7 Hz, 1H), 2.02–1.93 (m, 4H), 1.81 (s, 3H), 1.71 (dt, *J* = 14.6, 4.8 Hz, 2H), 0.88 (s, 3H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 138.6, 128.4, 127.5, 127.4, 93.3, 86.5, 82.3, 81.6, 80.4, 80.1, 73.9, 72.9, 61.0, 60.2, 59.1, 58.7, 40.2, 39.5, 32.6, 27.6, 23.8, 21.2, 13.7, 9.7; IR (neat) 2970, 2931, 1736 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{27}H_{42}O_8Na$ $[M + Na]^+$ 517.2777, found 517.2770.



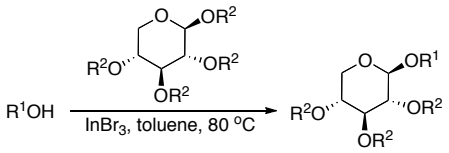
1-88



1-89

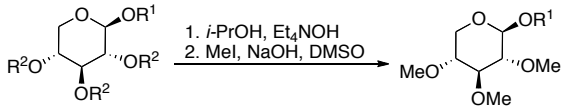
(2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxy-2-((2*S*,3*R*,4*S*,6*R*)-3-methyl-6-phenethyl-2-phenyltetrahydro-2*H*-pyran-4-yloxy)tetrahydro-2*H*-pyran (1-88) and (2*R*,3*R*,4*S*,5*R*)-3,4,5-trimethoxy-2-((2*S*,3*R*,4*S*,6*R*)-3-methyl-6-phenethyl-2-phenyltetrahydro-2H-pyran-4-yloxy)tetrahydro-2H-pyran (1-89). Following the general procedure for glycosylation with thioether **1-85**, (2*S*,3*R*,4*S*,6*R*)-3-methyl-6-phenethyl-2-phenyltetrahydro-2H-pyran-4-ol was transformed to THP **1-88** and **1-89**. **For THP 1-88**: Colorless oil; R_f = 0.33 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 5H), 7.31–7.24 (m, 2H), 7.18–7.14 (m, 3H), 4.30 (d, *J* = 7.6 Hz, 1H), 3.98 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.89 (d, *J* = 10.0 Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 3.47 (s, 3H), 3.41–3.36 (m, 2H), 3.28–3.23 (m, 1H), 3.09 (td, *J* = 8.9, 1.9 Hz, 2H), 2.98 (app. t,

J = 8.3 Hz, 1H), 2.75–2.65 (m, 2H), 2.16 (ddd, J = 12.6, 4.6, 1.3 Hz, 1H), 1.97–1.90 (m, 1H), 1.81–1.71 (m, 2H), 1.63 (q, J = 11.3 Hz, 1H), 0.78 (d, J = 11.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 140.9, 128.7, 128.44, 128.41, 128.0, 127.8, 125.8, 105.7, 85.6, 84.9, 84.0, 83.8, 79.5, 77.7, 74.8, 63.4, 60.9, 59.0, 43.8, 40.3, 37.6, 31.5, 13.3; IR (neat) 2927, 2831 cm^{-1}; HRMS (ES/MeOH) m / z calc for $C_{28}H_{38}O_6Na$ $[M + Na]^+$ 493.2566, found 493.2569. **For THP 1-89**: Colorless oil: R_f = 0.24 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.24 (m, 7H), 7.17–7.14 (m, 3H), 5.10 (d, J = 3.8 Hz, 1H), 3.90 (d, J = 10.1 Hz, 1H), 3.68 (dd, J = 11.0, 5.6 Hz, 1H), 3.62 (s, 3H), 3.57–3.40 (m, 3H), 3.51 (s, 3H), 3.48 (s, 3H), 3.42 (app. t, J = 9.2 Hz, 1H), 3.27–3.22 (m, 1H), 3.18 (dd, J = 9.6, 3.7 Hz, 1H), 2.75–2.66 (m, 2H), 2.14–2.10 (dd, J = 11.7, 7.6 Hz, 1H), 2.00–1.90 (m, 2H), 1.83–1.78 (m, 1H), 1.44 (q, J = 11.5 Hz, 1H), 0.78 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 140.8, 128.6, 128.5, 128.4, 128.0, 127.9, 125.9, 91.6, 85.0, 82.6, 81.7, 80.0, 76.3, 74.6, 61.2, 60.0, 59.2, 59.0, 42.4, 37.7, 35.8, 31.6, 14.1; IR (neat) 2924, 2854 cm^{-1}; HRMS (ES/MeOH) m / z calc for $C_{28}H_{38}O_6Na$ $[M + Na]^+$ 493.2566, found 493.2558.



General Procedure for Glycosylation with Ester Protected Xylose. Indium tribromide (0.06 mmol) and sugar **1-83** (or **1-102**) (0.40 mmol) dissolved in 0.65 mL toluene was added to a microwave vial containing alcohol (0.13 mmol). The resulting solution was irradiated in a CEM Discovery microwave synthesizer set at 80°C and 100W with air cooling for 1 minute. The crude mixture was concentrated *in vacuo*. Purification by column chromatography (1:9 EtOAc:hexanes) of the resulting crude residue afforded desired glycoside. Compounds

synthesized via this route were never fully characterized once we realized that cyanolide A was not biologically active.



General Procedure for Methylated Glycoside. Isopropanol (0.30 mL) and Et_4NOH (40. μL of 20% aq. solution) was added to a vial containing pivalated glycoside (0.012 mmol). The reaction was stirred over 7 days at room temperature, Et_4NOH (40. μL) was add on the second and fifth day. The base was neutralized by addition of Amberlite IR-120. The solution was filtered, the resin was washed with water and methanol and the combined filtrate were evaporated to dryness. The resulting mixture was run through a silica plug (10% MeOH/CH_2Cl_2) and concentrated *in vacuo*. The mixture was dissolved in 30. μL of DMSO and 5.0 μL of NaOH (50% aq. solution). The solution was stirred for 15 min and methyl iodide (0.17 mmol, 10. μL) was added under argon. The reaction mixture was stirred 3 h and then H_2O (1 mL) and CH_2Cl_2 (2 mL) were added. The solution was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded desired methylated glycoside. Compounds synthesized via this route were never fully characterized once we realized that cyanolide A was not biologically active.

References

[1] Pereira, A. R.; McCue, C. F.; Gerwick, W. H. *J. Nat. Prod.* **2010**, *73*, 217–220.

[2] Ross, A. G.; Bartley, P. B.; Sleigh, A. C.; Olds, G. R.; Li, Y.; Williams, G. M.; McManus, D. P. *N. Engl. J. Med.* **2002**, *346*, 1212–1220.

[3] (a) Steinmann, P.; Keiser, J.; Bos, R.; Tanner, M.; Utzinger, J. *Lancet Infect. Dis.* **2006**, *6*, 411–425. (b) Chitsulo, L.; Engels, D.; Montresor, A.; Savioli, L. *Acta Trop.* **2000**, *77*, 41–51.

[4] (a) World Health Organization. *Report of the Scientific Working Group Meeting on Schistosomiasis*, Geneva, Switzerland, Nov 14–16, 2005. (b) Gryseels, B.; Polman, K.; Clerinx, J.; Kestens, L. *Lancet* **2006**, *368*, 1106–1118.

[5] (a) Cioli, D.; Pica-Mattoccia, L. *Parasitol. Res.* **2003**, *90*, S3–S9. (b) Bergquist, R. *Acta Trop.* **2008**, *108*, 65–68. (c) Melman, S. D.; Steinauer, M. L.; Cunninghamn, C.; Kubatko, L. S.; Mwangi, I. N.; Wynn, N. B.; Mutuku, M. W.; Karanja, D. M. S.; Colley, D. G.; Black, C. L.; Secor, W. E.; Mjoki, G. M.; Loker, E. S. *PLOS Neglected Trop. Dis.* **2009**, *3*, No. e504.

[6] From: Center of Disease Control. CDC - Schistosomiasis. http://www.cdc.gov/parasites/schistosomiasis/biology.html (Accessed March 30, 2015), used with permission.

[7] Andrews, P.; Thyssen, J.; Lorke, D. *Pharmacol. Ther.* **1982**, *19*, 245–295.

[8] Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880–2883.

[9] (a) Shiina, I.; Katoh, T.; Nagai, S.; Hashizume, M. *Chem. Rec.* **2009**, *9*, 305–320. (b) Schäckel, R.; Hinkelmann, B.; Sasse, F.; Kalesse, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1619–1622.

[10] Hajare, A. K.; Ravikumar, V.; Khaleel, S.; Bhuniya, D.; Reddy, D. S. *J. Org. Chem.* **2011**, *76*, 963–966.

[11] Ball, M.; Baron, A.; Bradshaw, B.; Omori, H.; MacCormick, S.; Thomas, E. J. *Tetrahedron Lett*. **2004**, *45*, 8737–8740.

[12] Evans, D. A.; Hoveyda, A. H. *J. Org. Chem*. **1990**, *55*, 5190–5192.

[13] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989–1993.

[14] Yang, Z.; Xie, X.; Jing, P.; Zhao, G.; Zheng, J.; Zhao, C.; She, X. *Org. Biomol. Chem*. **2011**, *9*, 984–986.

[15] Evans, D. A.; Hoveda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447–6449.

[16] Petrier C.; Luche, J. L. *J. Org. Chem*. **1985**, *50*, 910–912.

[17] Pabbaraja, S.; Satyanarayana, K.; Ganganna, B.; Yadav, J. S. *J. Org. Chem*. **2011**, *76*, 1992–1925.

[18] (a) Srihari, P.; Rajendar, G.; Srinivasa Rao, R.; Yadav, J. S. *Tetrahedron Lett*. **2008**, *49*, 5590–5592. (b) Yadav, J. S.; Kumar, V. N.; Srinivasa Rao, R.; Srihari, P. *Synthesis* **2008**, 1938–1942. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem*. **2001**, *66*, 894–902. (d) Crimmins, M. T.; Emmitte, K. A. *Org. Lett*. **1999**, *1*, 2029–2032. (e) Hodge, M. B.; Olivo, H. F. *Tetrahedron* **2004**, *60*, 9397–9403.

[19] (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 5551–5553. (b) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett*. **1990**, *31*, 611–614. (c) Corey E. J.; Helal, C. J. *Angew. Chem., Int. Ed*. **1998**, *37*, 1986–2012.

[20] Gesinski, M. R.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2011**, *133*, 9727–9729.

[21] Deno, N. C. *J. Am. Chem. Soc*. **1947**, *69*, 2233–2234.

[22] (a) Zhang, Y.; Phillips, A. J.; Sammakia, T. *Org. Lett.* **2004**, *6*, 23–25. (b) Zhang, Y.; Sammakia, T. *J. Org. Chem.* **2006**, *71*, 6262–6265.

[23] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[24] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

[25] Sharpe, R. J.; Jennings M. P. *J. Org. Chem.* **2011**, *76*, 8027–8032.

[26] Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439.

[27] Waldeck, A. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 4470–4473.

[28] (a) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1636–1639. (b) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2011**, *13*, 1820–18323. (c) Fuwa, H.; Ichinokawa, N.; Noto, K.; Sasaki, M. *J. Org. Chem.* **2012**, *77*, 2588–2607. (d) Fuwa, H.; Noguchi, T.; Noto, K.; Sasaki, M. *Org. Biomol. Chem.* **2012**, *10*, 8108–8112.

[29] Bates, R. W.; Lek, T. G. *Synthesis* **2014**, *46*, 1731–1738.

[30] Compounds synthesized by Dr. Michael Gesinski. See reference 31.

[31] Gesinski, M. R. Ph.D. Dissertation, University of California, Irvine, 2011, pp. 1–198.

[32] Dalgard, J. E.; Rychnovksy, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662–15663.

[33] Williams, J. M.; Jobsen, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

[34] Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

[35] Malathong, V.; Rychnovsky, S. D. *Org. Lett.* **2009**, *11*, 4220–4223.

[36] (a) Chen, K.-M.; Hardtman, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett*. **1987**, *28*, 155–158. (b) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233–2238.

[37] Zhou, H.; Loh, T. *Tetrahedron Lett*. **2009**, *50*, 4368–4371.

[38] McDougal, P. G.; Rico, J. G.; Oh, Y.; Condon, B. D. *J. Org. Chem*. **1986**, *51*, 3388–3390.

[39] (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480–2482. (c) Huang, S.-L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297–299. (d) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185. (e) Tidwell, T. *Synthesis* **1990**, 857–871. (f) Freeman, F.; Kim, D. S. H. L. *J. Org. Chem*. **1992**, *57*, 1722–1727.

[40] Wang, J.; Chen, J.; Kee, C. W.; Tan, C.-H. *Angew. Chem., Int. Ed*. **2012**, *51*, 2382–2386.

[41] Under-oxidation of **1-76** led to the aldehyde and over-oxidation of the secondary alcohol led to the ketone.

[42] Csuk, R.; Schmuck, K.; Schafer, R. *Tetrahedron Lett*. **2006**, *47*, 8769–8770.

[43] Haider, A. F.; Williams, C. K. *J. Carbohydrate Chem*. **2007**, *26*, 411–418.

[44] Lopez, R.; Fernandez-Mayoralas, A. *J. Org. Chem*. **1994**, *59*, 737–745.

[45] Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun*. **2005**, 5097–5099.

[46] Tadpetch, K.; Rychnovsky, S. D. *Org. Lett*. **2008**, *10*, 4839–4842.

[47] Lefever, M. R.; Szabo, L. Z.; Anglin, B.; Ferracane, M.; Hogan, J.; Conney, L.; Polt, R. *Carbohydrate Research* **2012**, *351*, 121–125.

[48] (a) Harding, J. R.; King, C. D.; Perrie, J. A.; Sinnott, D.; Stachulski, A. V. *Org. Biomol. Chem*. **2005**, *3*, 1501–1507. (b) Purdie, T.; Irvine, J. C. *J. Chem. Soc., Trans*. **1903**, *83*, 1021–1037.

[49] ^{1}H NMR spectrum, ^{13}C NMR spectrum, IR spectrum, optical rotation, HPLC-DAD-MS/MS, and HRMS match for both isolated and synthetic cyanolide A

[50] Details of the repurification process and biological assays written by Dr. Karin Kleigrewere from the Gerwick group are attached in the Appendix. Used with permission.

[51] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J.; *Organometallics* **1996**, *15*, 1518–1520.

[52] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.*, **2002**, *124*, 12964–12965.

[53] (a) Marshal, J.; Van Devender, E. *J. Org. Chem.* **2001**, *66*, 8037–8041. (b) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440–11441.

Chapter 2

Silyl Enol Ether Prins Cyclization: Diastereoselective Formation of Substituted Tetrahydropyran-4-ones

Abstract: A diastereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyran-4-ones was developed. The key step of this methodology, a silyl enol ether Prins cyclization, was promoted by a condensation reaction between a hydroxy silyl enol ether and an aldehyde to afford substituted tetrahydropyran-4-ones. The cyclization was tolerant of many functional groups, and the modular synthesis of the hydroxy silyl enol ether allowed for the formation of more than thirty new tetrahydropyran-4-ones with up to 97% yield and >95:5 dr. The cyclization step forms new carbon–carbon and carbon–oxygen bonds, as well as a quaternary center with good diastereoselectivity. The method provides a versatile route for the synthesis of substituted tetrahydropyrans.

Introduction

Substituted tetrahydropyrans and tetrahydropyranones are a common motif in numerous biologically active natural products (Figure 2-1).[1] Synthesis of tetrahydropyran-4-ones (THPO's) followed by reduction of the ketone has been used to form 4-hydroxytetrahydropyran rings.[2]

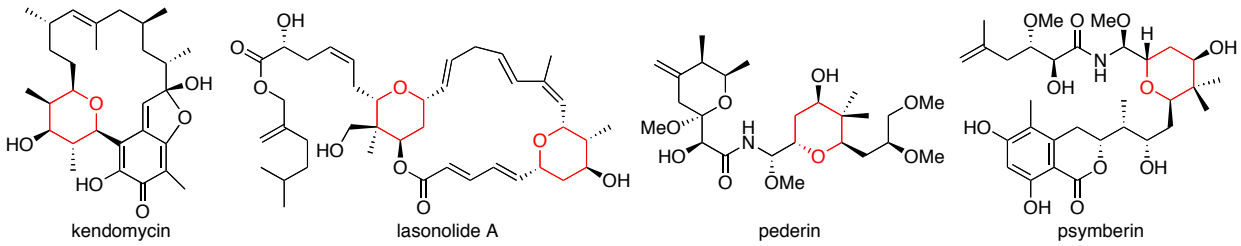


Figure 2-1. Biologically active natural products containing highly substituted tetrahydropyran rings such as kendomycin,[3] lasonolide A,[4] pederin,[5] and psymberin.[6]

Tetrahydropyranones are commonly prepared with carbon-carbon or carbon-oxygen bond forming reactions[7] by aldol-type cyclization,[8] hetero-Diels-Alder cycloaddition,[9] Japp-Maitland reaction,[10] oxa-Michael condensation,[11] and Petasis-Ferrier rearrangement (Figure 2-2).[12] These various methods have their strengths and limitations. For example, the hetero-Diels-Alder cycloaddition requires electronic matching of the diene and dienophile.[9] The Petasis-Ferrier rearrangement precursor is often obtained through olefination of an ester; this route would be incompatible with other unprotected carbonyl groups in the substrate. Because tetrahydropyrans are prevalent in natural products, the development of flexible new routes for their synthesis is an important goal. This chapter presents a full account of the silyl enol ether Prins cyclization for the synthesis of tetrahydropyranones.[13]

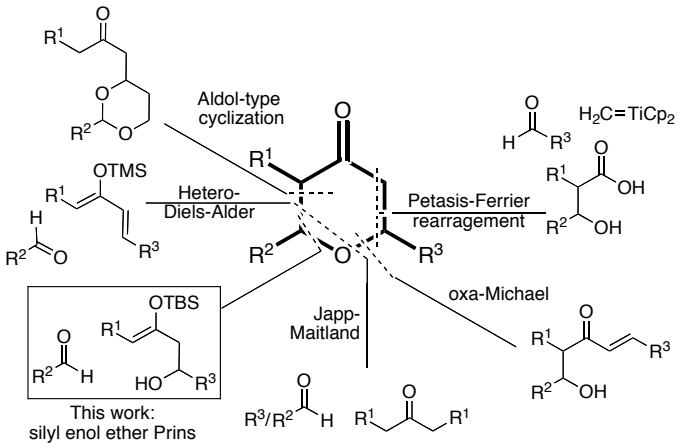
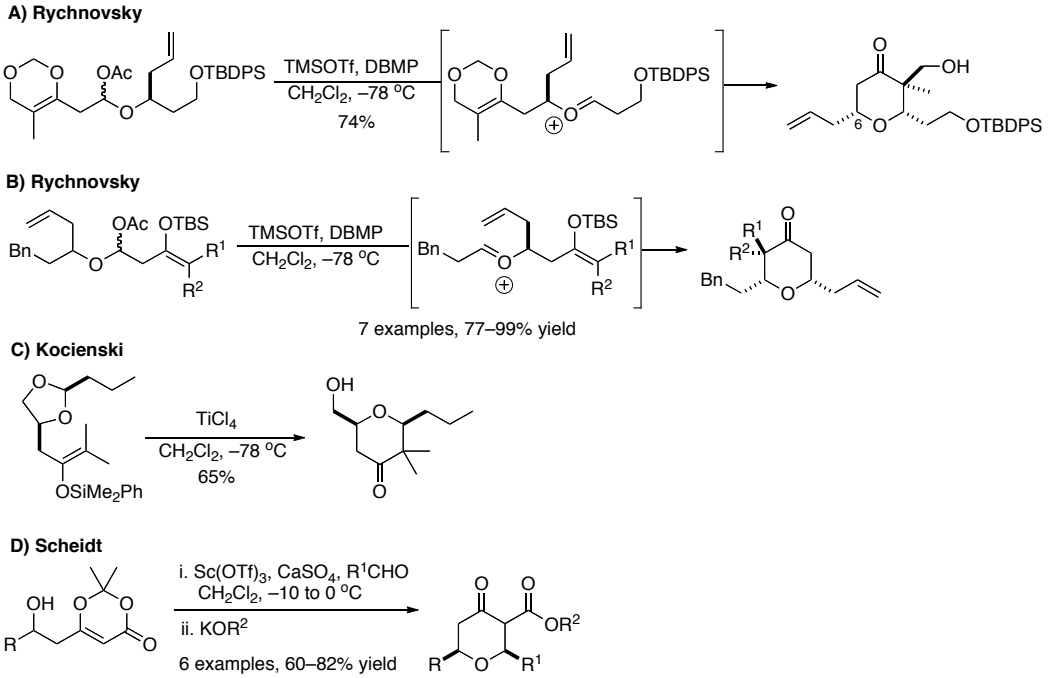


Figure 2-2. Common methods for forming tetrahydropyran-4-ones and the silyl enol ether Prins cyclization method discussed in this chapter

A variety of synthetic methods focused on the preparation of tetrahydropyran-4-ones utilizing an enol ether and oxocarbenium ion have been reported.[14-17] Previous work in the Rychnovsky group resulted in the development of an oxonia-Cope Prins cascade to form tetrahydropyran-4-ones (Scheme 2-1 A and B). This transformation involved the formation of an oxocarbenium ion followed by an oxonia-Cope rearrangement that revealed another oxocarbenium ion that underwent a Prins cyclization with the nearby enol ether.[15] The Kocienski group reported an intramolecular Mukaiyama reaction where a protected aldehyde was deprotected to form an oxocarbenium ion that was attacked by a tethered silyl enol ether to form a THPO (Scheme 2-1 C).[16] Scheidt utilized a dioxinone as a nucleophilic enol ether in a Prins cyclization (Scheme 2-1 D).[17] Although existing methods to prepare tetrahydropyran-4-ones with an enol ether and oxocarbenium ion are known, each example resulted in a specific functional group on the ring that helped facilitate the reaction. For example, the oxonia-Cope Prins always resulted in an allyl group at the C-6 position of the product. We envisioned a method that would enable the formation of tetrahydropyran-4-ones with the ability to vary functional groups appended to all positions of the THPO core.

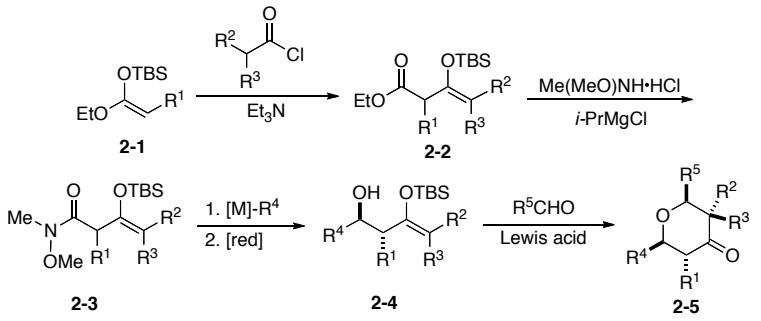
Scheme 2-1. Select examples of tetrahydropyran-4-one synthesis from an enol ether and oxocarbenium ion[18]



After the successful total synthesis of cyanolide A (Chapter 1) utilizing a diastereoselective synthesis of a THPO through cyclization between a hydroxy silyl enol ether and an aldehyde, we decided to further develop the method scope.[13] We explored the diastereoselectivity and functional group tolerance of this silyl enol ether Prins cyclization,[19] as well as the scope with different substitution patterns. An overview of the tetrahydropyran-4-one synthesis is shown in Scheme 2-2. The synthesis began with deprotonation of an acid chloride using triethylamine to form a ketene in situ that, when reacted with silyl ketene acetal **2-1**,[20] produced ester **2-2**. Ester **2-2** was transformed to Weinreb amide **2-3**.[21] Addition of a nucleophilic organometallic reagent and subsequent reduction of the resulting ketone afforded alcohol **2-4**. Silyl enol ether Prins cyclization of alcohol **2-4** with a Lewis-acid-activated aldehyde produced desired THPO **2-5** with high diastereoselectivity. The thermodynamically favored cyclization is very effective for introducing quaternary centers at the C-3 position of the

THPO. This method allows for the formation of highly functionalized tetrahydropyran-4-ones with substituents at each carbon atom of the THPO core.

Scheme 2-2. General overview of this method for diastereoselective THPO synthesis

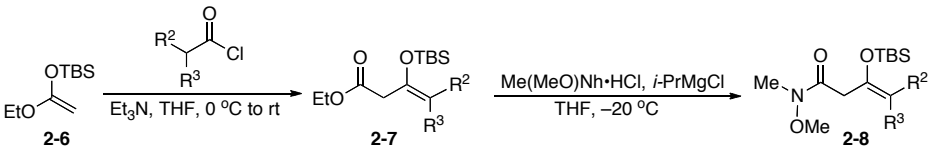


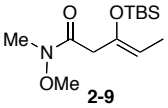
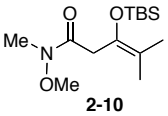
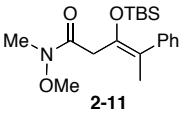
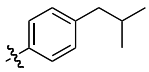
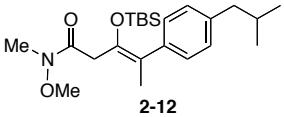
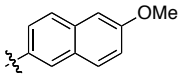
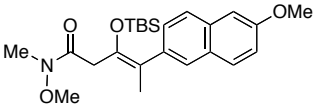
Results

Synthesis of Weinreb Amide Intermediates

The syntheses of a variety of Weinreb amides are presented in Table 2-1. The formation of ester **2-7** occurred in satisfactory yields by reacting the ketene, prepared in situ by deprotonation of the acid chloride, with silyl ketene acetal **2-6**.[22] Dimethyl ketene (entry 2), which would come from the least acidic acid chloride, was prepared by zinc reduction of 2-bromo-2-methylpropionyl bromide.[23] In entry 3, no desired ester was observed due to the instability of the unsubstituted silyl enol ether product. The acid chloride precursors from entries 5 and 6 were prepared from the non-steroidal anti-inflammatory drugs, ibuprofen and naproxen, respectively, demonstrating that motifs present in biologically active molecules can be incorporated into the THPO using this method. Acid chlorides with an aryl group for R^2 and a proton for R^3 generally led to low yields of ester **2-7** (entry 7); these esters were not taken further in the sequence. The transformation to ester **2-7** was highly diastereoselective; ketene acetal **2-6** underwent nucleophilic addition at the less hindered face of the ketene. Only a single alkene isomer of Weinreb amide **2-8** was isolated. The configuration with the larger R^2 substituent *cis* to the -OTBS group was favored in each case.

Table 2-1. Preparation of Weinreb amides **2-9**–**2-13**



entry	R^2	R^3	yield (%) ketene addition	yield (%) amide formation	product
1	Me	H	77%	84%	 **2-9**
2[a]	Me	Me	60%[a]	83%	 **2-10**
3	H	H	decomp.	—	—
4	Ph	Me	81%	83%	 **2-11**
5		Me	70%	76%	 **2-12**
6		Me	87%	90%	 **2-13**
7	Ph	H	31%	—	—

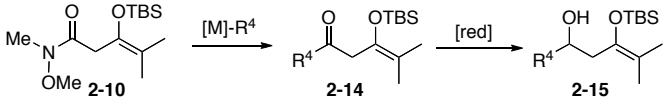
[a] The dimethylketene reagent was prepared in situ by zinc reduction of 2-bromo-2-methylpropionyl bromide.

Synthesis of Hydroxy Silyl Enol Ether Precursor

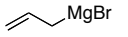
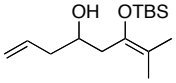
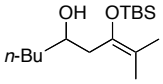
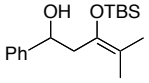
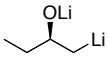
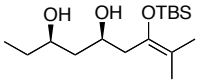
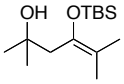
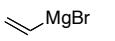
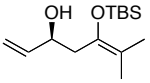
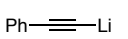
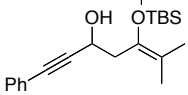
Weinreb amide **2-10** underwent nucleophilic addition with a variety of Grignard and organolithium reagents to yield ketone **2-14** (Table 2-2). Modest yields were observed with smaller nucleophiles (entry 7) due to deprotection of the product by nucleophilic attack on the silyl group.[24] Direct reduction of the crude allylic ketone (entry 1) was necessary to prevent isomerization of the double bond into conjugation with the ketone. Reduction of an α,β-unsaturated ketone (entry 6) could be achieved in high yields with a Luche reduction, or enantioselectively with a CBS reduction (9:1 e.r.)[25] The β-oxy-alkyllithium reagent[26] from entry 4 was enantioenriched, and *syn*-selective reduction[27] of the ketone resulted in diol **2-19** as a

single diastereomer. Tertiary alcohol **2-20** was obtained by double addition of methylmagnesium bromide into ester **2-7** (R^2 and R^3 = Me). A wide variety of hydroxy silyl enol ethers were prepared by this sequence.

Table 2-2. Preparation of hydroxy silyl enol ether from amide **2-10**



2-10 **2-14** **2-15**

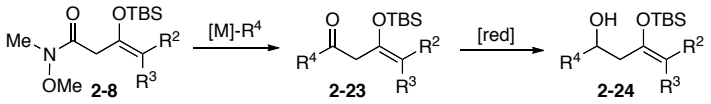
entry	[M]-R^4	yield (%) 1,2 addition	yield (%) reduction	product
1		–	47%[a]	 **2-16**
2	*n*-BuLi	82%	92%[b]	 **2-17**
3	PhMgBr	73%	85%[b]	 **2-18**
4		82%	80%[c] (9.8:0.2 *e.r.*)	 **2-19**
5	MeMgBr	66%[d]	–	 **2-20**
6		67%	94%[e] 60%[f] (9.0:1.0 *e.r.*)	 **2-21**
7		39%	87%[b]	 **2-22**

[a]Crude ketone was directly reduced with DIBAL-H. The alcohol was obtained through a:
[b]$NaBH_4$ reduction, [c]$NaBH_4$ reduction with $Et_2B(OMe)$ additive, [d]double addition to ester **2-7**,
[e]Luche reduction, [f]CBS reduction

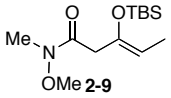
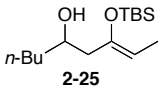
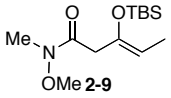
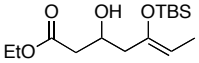
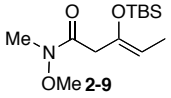
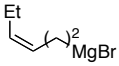
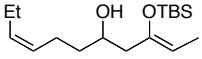
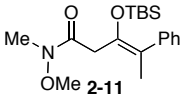
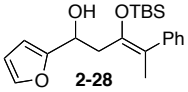
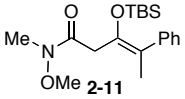
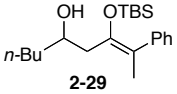
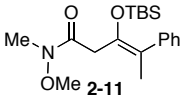
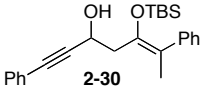
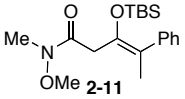
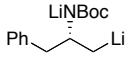
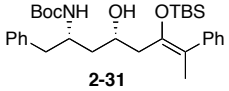
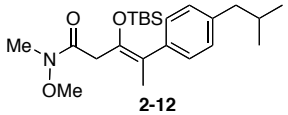
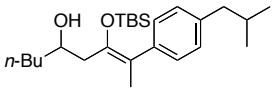
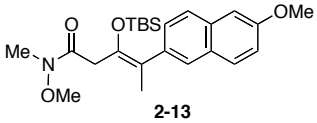
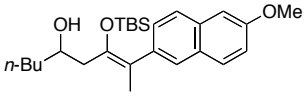
Transformation of Weinreb amides with varying R^2 and R^3 substituents to the corresponding alcohols are shown in Table 2-3. Addition of Grignard or organolithium reagents to Weinreb amide **2-8** gave desired ketone **2-23**. When treated with organolithium reagents, isomerization of less substituted silyl enol ether **2-9** to form the conjugated silyl enol ether was observed as a side reaction. The β-amino-alkyllithium reagent from entry 7 was synthesized from enantiopure L-phenylalanine. *Syn*-selective reduction[28] of the resulting ketone with L-selectride resulted in amino alcohol **2-31** as a single diastereomer. Reduction of ketone **2-23** with sodium

borohydride occurred in good yield to give racemic hydroxyl silyl enol ethers **2-25**–**2-30**, **2-32**, **2-33**.

Table 2-3. Preparation of the hydroxy silyl enol ether with varying R^2 and R^3 substituents



2-8 **2-23** **2-24**

entry	amide	[M]-R^4	yield (%) 1,2 addition	yield (%) reduction[a]	product
1	 **2-9**	*n*-BuLi	66%	91%	 **2-25**
2	 **2-9**		59%	96%	 **2-26**
3	 **2-9**		75%	85%	 **2-27**
4	 **2-11**		87%	quant.	 **2-28**
5	 **2-11**	*n*-BuLi	78%	84%	 **2-29**
6	 **2-11**		58%	63%	 **2-30**
7	 **2-11**		85%	56%[b]	 **2-31**
8	 **2-12**	*n*-BuLi	73%	97%	 **2-32**
9	 **2-13**	*n*-BuLi	60%	79%	 **2-33**

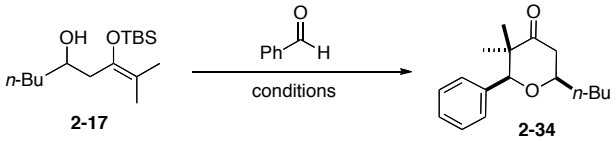
[a]$NaBH_4$ reduction, [b]L-selectride reduction

Optimization of the Silyl Enol Prins Cyclization

For the synthesis of cyanolide A (Chapter 1), a variety of Lewis acids were examined to determine the best activator for the silyl enol Prins reaction. Cyclization of hydroxyl silyl enol ethers with aromatic and conjugated aldehydes was shown to be most effective with BF_3•OEt_2,

while TMSOTf was necessary for aliphatic aldehydes.[13a] A new optimization of the THPO cyclization reaction was performed with hydroxyl silyl enol ether **2-17**, benzaldehyde, and BF_3•OEt_2 (Table 2-4). It was determined that a polar solvent was necessary for reactivity (entries 1–3). No product was observed when the reaction was run in toluene (entry 2). Dichloromethane (DCM) or acetonitrile (MeCN) as the solvent resulted in similar yields, 66% and 65% respectively, after four hours. Dichloromethane was selected as the solvent of choice due to its ease of removal after the cyclization. Reaction concentrations were also examined, with concentrations of 0.1 M, 0.4 M and 1.0 M of alcohol **2-17** evaluated (entry 4–6). It was found that the most concentrated mixture, 1.0 M, gave the highest yield of 69%. Optimization of temperature, equivalents of the aldehyde, and equivalents of Lewis acid were conducted using Design of Experiments (DoE).[29] Yields were improved at lower temperatures: reactions at –95 ºC

Table 2-4. Optimization of the THPO cyclization reaction with hydroxy silyl enol ether **2-17** and benzaldehyde



entry	temp	equiv of PhCHO	equiv of BF_3•OEt_2	solvent	conc (M)	% yield[a]
1	–78 ºC	3.0	3.0	DCM	0.4	66
2	–78 ºC	3.0	3.0	toluene	0.4	no rxn
3	–78 ºC	3.0	3.0	MeCN	0.4	65
4	–95 ºC	3.0	2.0	DCM	1.0	69
5	–95 ºC	3.0	2.0	DCM	0.5	46
6	–95 ºC	3.0	2.0	DCM	0.1	48
7	–95 ºC	4.5	1.5	DCM	0.4	71
8	–95 ºC	1.5	1.5	DCM	0.4	71
9	–95 ºC	4.5	4.5	DCM	0.4	74
10	–95 ºC	1.5	4.5	DCM	0.4	63
11	–40 ºC	4.5	1.5	DCM	0.4	51
12	–40 ºC	1.5	1.5	DCM	0.4	49
13	–40 ºC	4.5	4.5	DCM	0.4	50
14	–40 ºC	1.5	4.5	DCM	0.4	62
15	–78 ºC	1.5	1.5	DCM	1.0	69
16[b]	–78 ºC	1.5	1.5	DCM	0.5	48

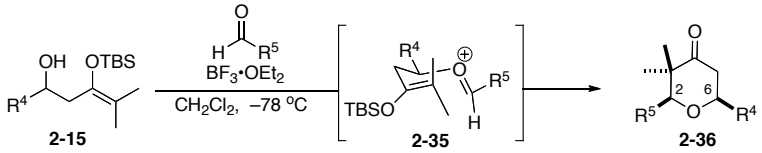
[a] Yields were determined by ^{1}H NMR spectroscopy with respect to mesitylene internal standard. [b] A diluted solution of silyl enol ether was added dropwise to a solution of aldehyde and BF_3•OEt_2 at –78 ºC.

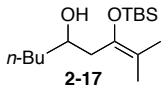
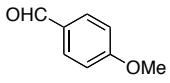
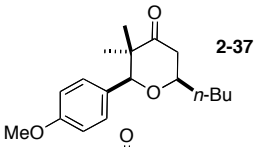
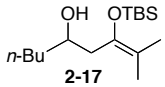
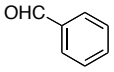
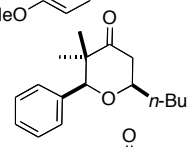
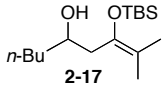
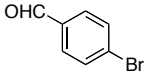
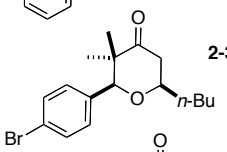
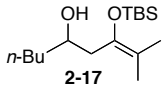
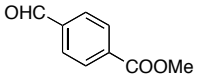
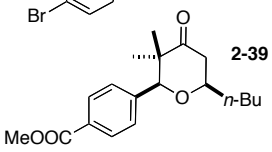
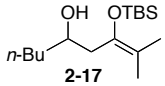
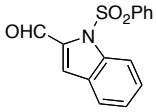
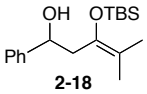
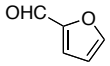
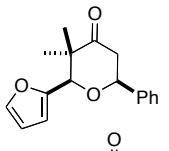
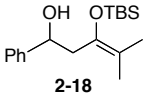
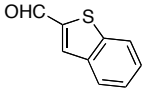
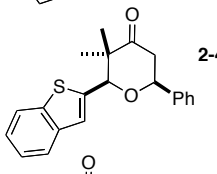
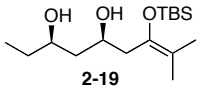
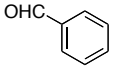
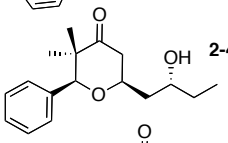
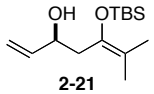
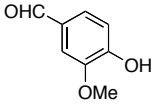
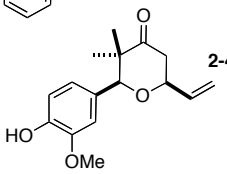
gave slightly higher yields but were much slower. Cyclization reactions shown herein were conducted at –78 ºC for ease of operation. Excess BF_3•OEt_2 relative to the aldehyde lowered yields (entry 10), and a 1:1 molar ratio was found to be optimal. It was found that a large excess of both BF_3•OEt_2 and aldehyde minimally affected the yields (entry 9). Dropwise addition of hydroxyl silyl enol ether **2-17** to a solution of aldehyde and Lewis acid lowered the yield (entry 16). After optimization of the cyclization was complete, the silyl enol ether Prins reaction for the rest of this chapter was carried out at –78 ºC in 1.0 M dichloromethane with 1.5 equivalents of both the Lewis acid and aldehyde relative to the alcohol.

*Silyl Enol Ether Prins Cyclization with Alcohol **2-15***

The tetrahydropyran-4-one synthesis with aromatic aldehydes is shown in Table 2-5. Electron rich aldehydes gave higher yields than electron poor aldehydes (entry 1–4), possibly due to enhanced stabilization of oxocarbenium ion intermediate **2-35**. This cyclization reaction is compatible with heterocycles such as furans (entry 6) and benzothiophenes (entry 7), but no reaction occurred with sulfonate-protected indole carboxaldehyde (entry 5).[30] Indole carboxaldehyde[31] and 2-pyridinecarboxaldehyde were also tested as the aldehyde partner in the cyclization, but only starting material was recovered. This lack of reactivity may be contributed to the irreversible binding of the Lewis acid to the nitrogen atom. The reaction conditions are tolerant of free aliphatic and aromatic alcohols (entry 8 and 9), esters (entry 4), and aryl halides (entry 3). Only the THPO 2,6-*cis* diastereomer was observed when starting with hydroxyl silyl enol ether **2-17**–**2-21**.

Table 2-5. Scope of the tetrahydropyran-4-one synthesis with hydroxyl silyl enol ether **2-15** and aromatic aldehydes[18]

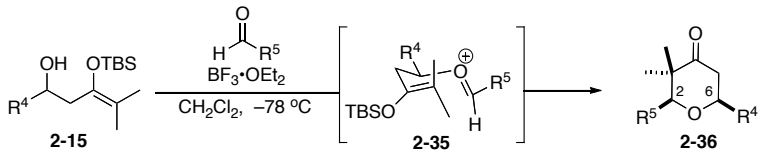


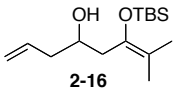
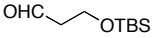
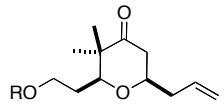
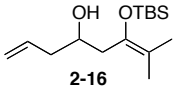
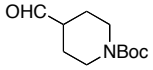
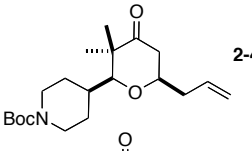
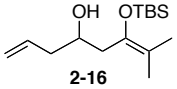
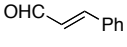
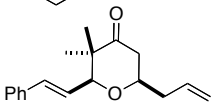
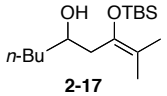
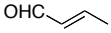
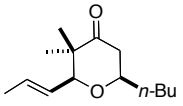
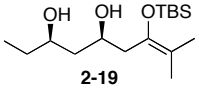
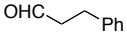
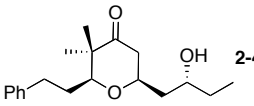
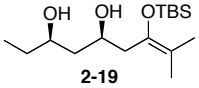
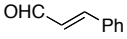
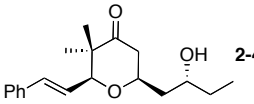
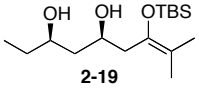
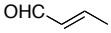
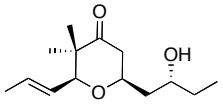
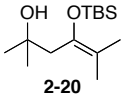
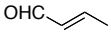
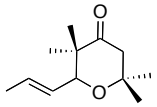
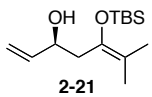
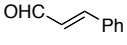
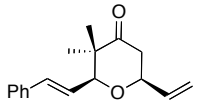
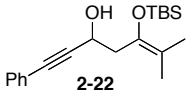
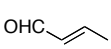
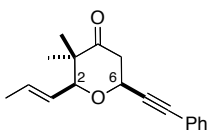
entry	alcohol	aldehyde	product	yield (%)
1	 **2-17**		 **2-37**	69%
2	 **2-17**		 **2-34**	47%
3	 **2-17**		 **2-38**	43%
4	 **2-17**		 **2-39**	35%
5	 **2-17**		–	no rxn
6	 **2-18**		 **2-40**	63%
7	 **2-18**		 **2-41**	38% (95% BRSM)
8	 **2-19**		 **2-42**	64%
9	 **2-21**		 **2-43**	30%

The cyclization reaction was also compatible with aliphatic and conjugated aldehydes (Table 2-6). Conjugated aldehydes are especially good substrates and generated clean products in high yields (entry 3 and 6). These aldehydes are expected to form resonance stabilized

oxocarbenium ion intermediates, which appear to facilitate the cyclization. The difference between aliphatic and conjugated aldehydes is especially apparent when comparing entry 5 and 6. Aliphatic aldehydes also required a stronger Lewis acid, TMSOTf, to facilitate the cyclization

Table 2-6. Scope of the tetrahydropyran-4-one synthesis with hydroxy silyl enol ether **2-15** and conjugated and aliphatic aldehydes[18]



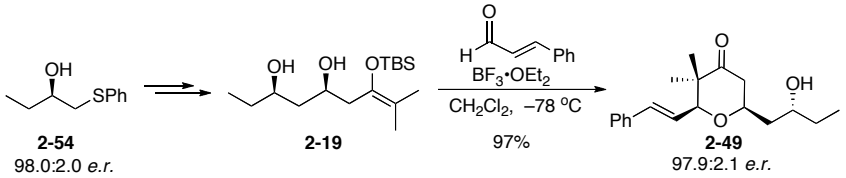
entry	alcohol	aldehyde	product		yield (%)
1[a]	 **2-16**			**2-44**	76% R = TBS:H 1:1.7
2[a]	 **2-16**			**2-45**	42%
3	 **2-16**			**2-46**	91%
4	 **2-17**			**2-47**	73%
5[a]	 **2-19**			**2-48**	56%
6	 **2-19**			**2-49**	97%
7	 **2-19**			**2-50**	65%
8	 **2-20**			**2-51**	80%
9	 **2-21**			**2-52**	62%
10	 **2-22**			**2-53**	71% (4.1: 1.0 *cis:trans*)

[a] TMSOTf was used as the Lewis acid instead of BF_3•OEt_2.

(entry 5). The silyl enol ether Prins reaction is tolerant of Boc-protected amines (entry 2). Tertiary alcohol **2-20** resulted in THPO **2-51** with two tetrasubstituted carbons (entry 8). A silyl protected alcohol (entry 1) was partially deprotected under the cyclization reaction conditions. Optimized procedures were found to allow for deprotection or retention of the silyl protected alcohols. Full deprotection of the silyl group was achieved by removing the reaction mixture from its –78 ºC bath and stirring for a few minutes before quenching with sodium bicarbonate. Retention of the silyl group was achieved by adding a bulky base additive, 2,6-di-*tert*-butyl-4-methylpyridine, to neutralize the triflic acid formed during the reaction. Cyclization of hydroxy silyl enol ether **2-22** with crotonaldehyde led to a 4.1:1.0 ratio of the 2,6-*cis* and 2,6-*trans* THPO product. Cyclizations with a variety of aldehydes and alcohols **2-16**–**2-21** resulted in only a single diastereomer. The origin of the diastereoselectivity in the cyclization with hydroxy silyl enol ether **2-22** will be considered in the discussion section.

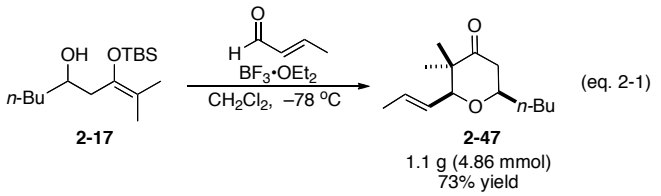
Enantiomerically enriched THPOs can be synthesized using this route (Scheme 2-3).[13] THPO **2-49** was synthesized from enantiomerically enriched alcohol precursor **2-19**. The enantiomeric ratio of thioether **2-54**, obtained from epoxide opening with thiophenol, was 98.0:2.0. The enantiomeric ratio of THPO **2-49** was 97.9:2.1 and the enantiospecificity of the reaction was >99%, demonstrating that essentially no optical activity was lost during the cyclization reaction.[32]

Scheme 2-3. Enantiomeric ratio is retained throughout the cyclization



The scalability of the cyclization reaction was explored with alcohol **2-17** (eq. 2-1). Reacting crotonaldehyde with 1.9 g (6.7 mmol) of alcohol **2-17** produced THPO **2-47** in 73%

yield as a single diastereomer. The reaction was completed after four hours at –78 ºC. This result indicates that no significant loss in yield[33] was observed at a scale useful in multistep syntheses.

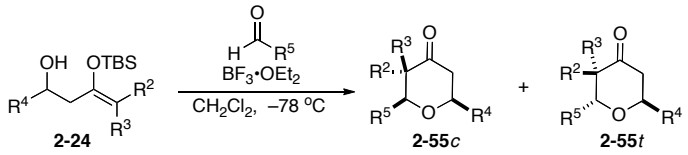


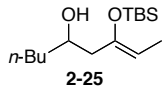
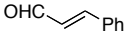
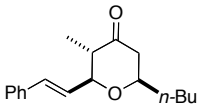
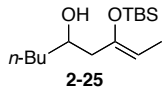
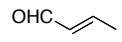
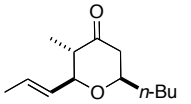
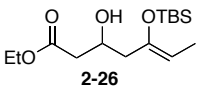
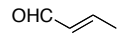
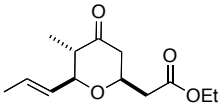
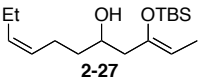
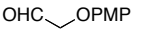
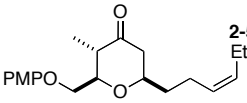
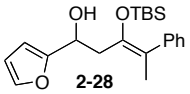
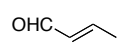
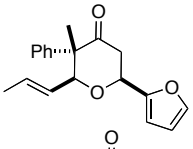
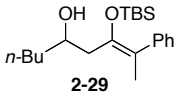
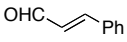
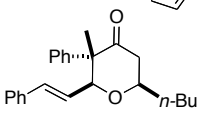
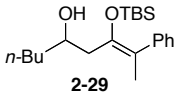
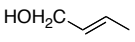
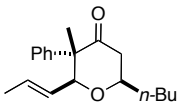
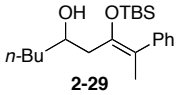
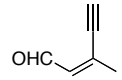
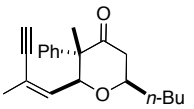
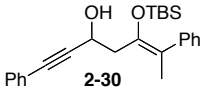
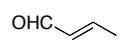
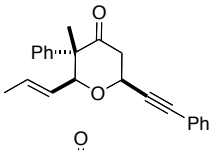
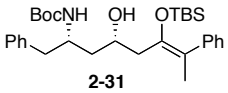
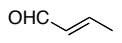
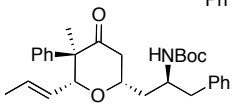
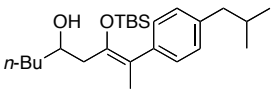
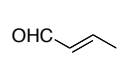
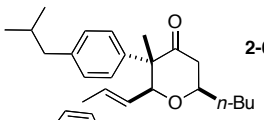
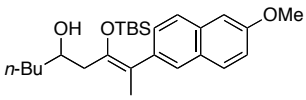
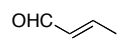
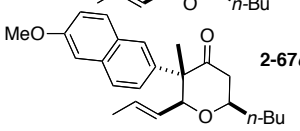
(eq. 2-1)

*Silyl Enol Ether Prins Cyclization with Alcohol **2-24***

The tetrahydropyran-4-ones described to this point have been dimethyl substituted at the C-3 position. Table 2-7 shows examples with a variety of different substituents on the silyl enol ether. These silyl enol ethers often resulted in a mixture of 2,6-*cis* and 2,6-*trans* diastereomers; when the C-3 was dimethyl substituted, usually only a single diastereomer was observed by ^{1}H NMR. The cyclization reactions with unsymmetric silyl enol ethers form two new stereocenters during the cyclizations, one of them at a quaternary carbon. Substituents R^2 = methyl and R^3 = hydrogen (entries 1–4) were examined because many THP(O) natural products contain a single methyl group at the C-3 position.[1] Lower THPO yields were obtained with hydroxy silyl enol ether **2-25** because this monosubstituted silyl enol ether underwent the competitive intermolecular Mukaiyama aldol addition, presumably due to the fact that **2-25** is less sterically hindered at the enol ether moiety than other hydroxy silyl enol ether cyclization partners. The cyclization was compatible with ester groups and protected primary amines (entry 3 and 10). Alkene geometries on the aldehyde were unchanged under the cyclization reaction conditions even though a conjugated oxocarbenium ion was formed; THPO **2-63** was synthesized with a 5:1 *Z:E* mixture of the aldehyde[34] and the same *Z:E* ratio was obtained after the reaction. Similar to THPO **2-53** (Table 2-6, entry 10), the small alkyne substituent on the alcohol led to a loss of

Table 2-7. Scope of the tetrahydropyran-4-one synthesis with different aldehydes and alcohols, with varying substituents at the C-3 position



entry	alcohol	aldehyde	product		yield (%)
1	 **2-25**			**2-56*c***	40% (8.3:1:0 *cis:trans)*
2	 **2-25**			**2-57*c***	30% (7.0:1.0 *cis:trans)*
3	 **2-26**			**2-58*c***	49% (5.6:1.0 *cis:trans*)
4[a]	 **2-27**			**2-59*c***	72% (3.3:1.0 *cis:trans)*
5	 **2-28**			**2-60*c***	62% (6.0:1:0 *cis:trans)*
6	 **2-29**			**2-61*c***	69% (8.2:1:0 *cis:trans)*
7	 **2-29**			**2-62*c***	82% (2.8:1.0 *cis:trans*)
8	 **2-29**	 (5:1 *Z:E*)		**2-63*c***	48% (5:1 *Z:E*) (>95::5 *cis:trans)*
9	 **2-30**			**2-64*c***	94% (1.7:1:0 *cis:trans*)
10	 **2-31**			**2-65*c***	76% (>95:5 *cis:trans*)
11	 **2-32**			**2-66*c***	50% (76% BRSM) (3.0:1.0 *cis:trans*)
12	 **2-33**			**2-67*c***	94% (3.1:1.0 *cis:trans*)

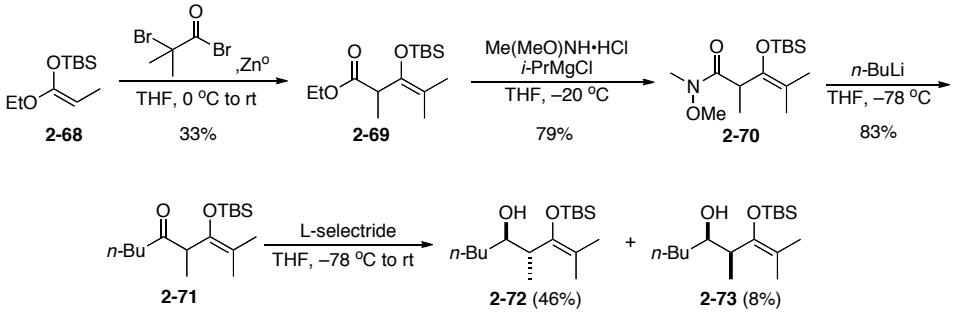
[a] TMSOTf was used as the Lewis acid instead of BF_3•OEt_2.

cis/*trans* diastereoselectivity (Table 2-7, entry 9). Hydroxy silyl enol ethers with substituted aromatic rings underwent cyclization successfully (entry 10 and 11).

Substitution at the C-5 Position on the THPO

The stereoselective outcome of the THPO cyclization reaction was further examined with substitution at C-5. The hydroxy silyl enol ether synthesis with substitution at C-5 is shown in Scheme 2-4. The synthesis began with zinc reduction of 2-bromo-2-methylpropionyl bromide to form dimethyl ketene in situ.[23] Dimethyl ketene was added to silyl ketene acetal **2-68** to afford ester **2-69**, which was transformed to Weinreb amide **2-70**. Addition of *n*-butyllithium resulted in ketone **2-71**, and diastereoselective reduction of **2-71** with L-selectride produced a mixture of *anti*-alcohol **2-72** (major) and *syn*-alcohol **2-73** (minor). The two diastereomers were isolated and used in separate THPO forming reactions.

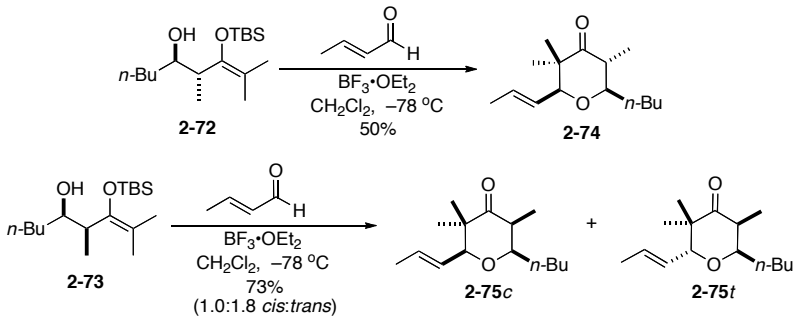
Scheme 2-4. Formation of the hydroxy silyl enol ether with R^1 = Methyl for substitution at C-5 in the resulting tetrahydropyran-4-one



Alcohol **2-72** underwent cyclization with crotonaldehyde to afford THPO **2-74** as a single diastereomer in 50% yield. All four substituents on the six membered ring occupied pseudo-equatorial positions in THPO **2-74** (Scheme 2-5). Cyclization of *cis*-alcohol **2-73** with crotonaldehyde resulted in a mixture of diastereomers, THPO **2-75***c* and **2-75***t*. This cyclization was the first in which the 2,6-*trans* THPO was the major product and the 2,6-*cis* THPO was the

minor product. An explanation for this reversal of selectivity is presented in the discussion section.

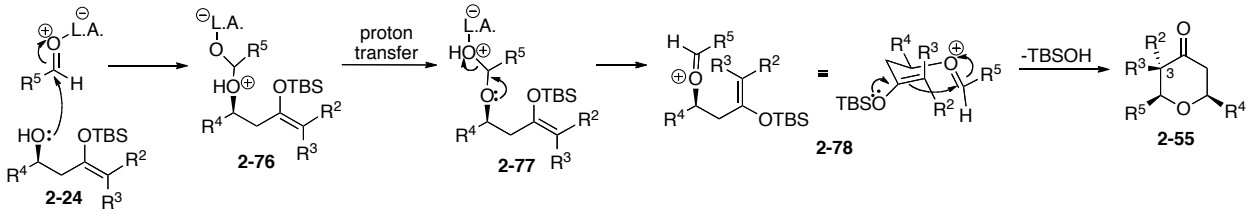
Scheme 2-5. Tetrahydropyran-4-one synthesis with substitution at C-5



Discussion

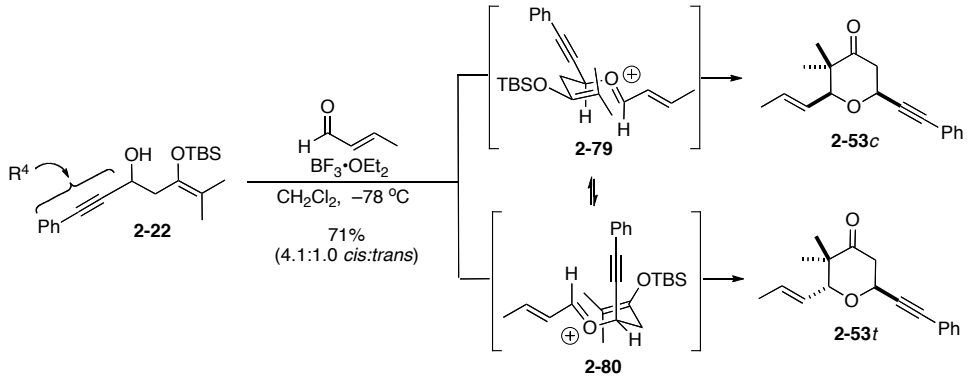
The proposed mechanism for the silyl enol ether cyclization is outlined in Scheme 2-6. The reaction begins with formation of hemiacetal **2-76** from alcohol **2-24** and the aldehyde, followed by expulsion of the leaving group to generate the key oxocarbenium ion intermediate **2-78**. These steps are presumably promoted by the Lewis acid. Irreversible[35] nucleophilic attack of the silyl enol ether onto the oxocarbenium ion followed by lost of the TBS group forms desired THPO **2-55**. A chair-like conformation with *E*-configuration at the oxocarbenium[36] is expected in the cyclization transition state. The configuration of the major product is consistent with this transition state geometry. Placement of the R^4 groups in the pseudo-equatorial position favors one of the two possible chair-like transitions states. The quaternary stereocenter at C-3 arises from the *Z*-configuration of the enol ether in the chair-like transition state. The sterically biased ketene addition (Table 2-1) results in the less bulky substituent at R^3 in enol ether **2-24**; the cyclization reactions places this substituent in the axial position at C-3 in the new tetrahydropyran-4-one ring. The stereochemical outcome of the silyl enol ether Prins cyclization is consistent with the expected chair-like transition state.

Scheme 2-6. Proposed mechanism for the silyl enol ether Prins cyclization



Silyl enol ether **2-22** (Table 2-6, entry 10 and Scheme 2-7) leads to a large amount of the 2,6-trans THPO product (**2-53***t*) in the cyclization with crotonaldehyde. The diastereoselectivity of the major product in the cyclization results from the alkyne and crotonaldehyde alkene being placed in the lower energy pseudo-equatorial position in the chair-like reactive conformer **2-79** (Scheme 2-7). When the R^4 substituent is sterically small, in this case an alkyne, the energetic cost for it to occupy pseudo-axial position in the reactive conformation **2-80** is modest, and the cyclization results in a significant amount of the 2,6-*trans* diastereomer **2-53***t*. For relative size comparison, an alkyne group has an A value of 0.41 kcal/mol and a methyl group has an A value of 1.7 kcal/mol in a cyclohexane ring.[37]

Scheme 2-7. Small R^4 groups resulted in diminished diastereoselectivity during cyclization



The 2,6-*cis*/*trans* selectivity was also influenced by the substituents on the C-3 position (Figure 2-3). When the substituents on C-3 are identical, THPO **2-47** was observed as a single diastereomer with a 2,6-*cis* configuration. When there was a methyl group and proton on C-3, a 7.0:1.0 *cis*:*trans* diastereomeric ratio was obtained (THPO **2-57**). With aryl and methyl

substitution on C-3 (THPO **2-62**, **2-66**, and **2-67**), diastereoselectivity further diminished to about a 3:1 ratio of *cis*:*trans* diastereomers. Note that in all of these examples the larger group (R^2) occupied the equatorial position at C-3 in the 2,6-*cis* product. Interestingly, the minor diastereomer in this cyclization reaction is not the same one reported for similar cyclizations, an oxonia-cope Prins reaction.[38] Dalgard and Rychnovsky reported the C-3 epimer of the 2,6-*cis* product as the minor diastereomer in their systems, and suggest that the minor product could arise from *E*/*Z* isomerization of the starting silyl enol ether[39] or a competing chair–boat cyclization.[1a] Our minor diastereomer had a different relative stereochemical relationship between C-2 and C-6 and retained relative stereochemistry between C-2 and C-3; we proposed that the minor diastereomer would arise through the diastereomeric chair-like transition state **2-82** (Figure 2-3). One would expect that as the size of the R^2 group increases, the steric interactions between the R^2 substituent and the –OTBS and crotyl group in TS **2-81** would increase. TS **2-82** places the R^2 substituent axial, relieving steric interactions between the crotyl group, and becomes more favorable as the size of the R^2 substituent relative to R^3 substituent increases. Thus, increasing the difference in size between the large R^2 and small R^3 subsitutents would lead to more of the 2,6-*trans* diastereomer, which is the observed outcome in this series.

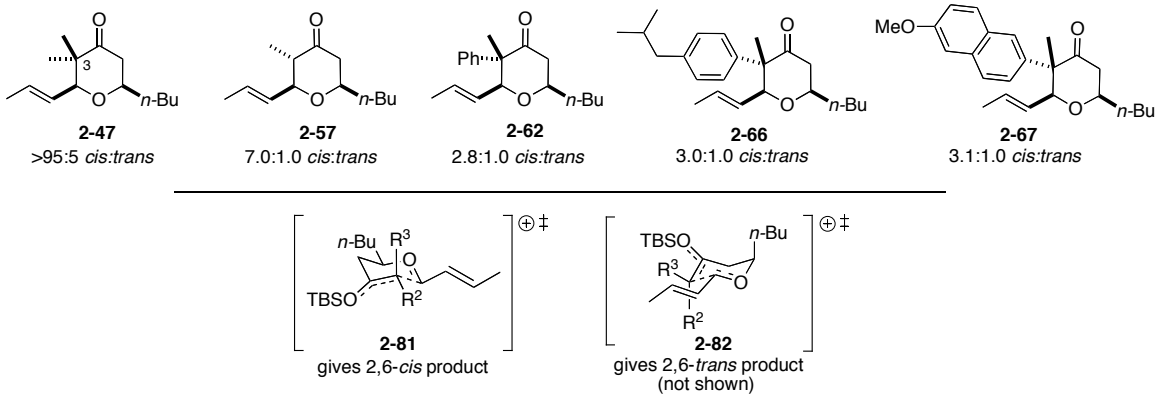
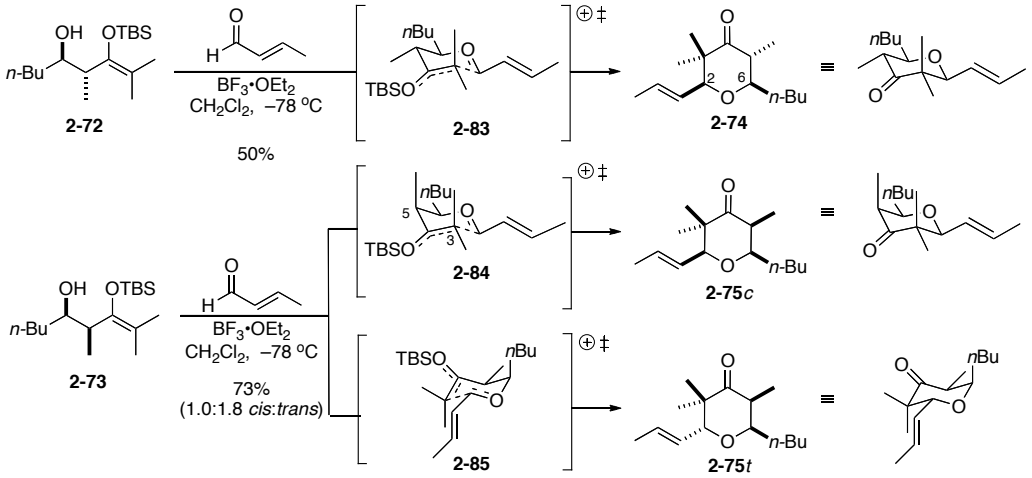


Figure 2-3. The diastereoselective trend caused by varying the substituents at C-3 is shown with the major 2,6-*cis* isomer drawn. The minor diastereomer has a 2,6-*trans* relationship. The relative stereochemistry between C-2 and C-3 remained the same for both diastereomers.

Introducing a new stereogenic center at C-5 influenced the selectivity of the cyclization (Scheme 2-5 and Scheme 2-8). When alcohol **2-72** reacted with crotonaldehyde, it likely proceeded through chair-like transition state **2-83** where all possible substituents adopted pseudo-equatorial positions (Scheme 2-8). In contrast, the cyclization geometry from the reaction of alcohol **2-73** and crotonaldehyde must have at least one substituent axial. Disfavored transition state **2-84** has the C-5 methyl group in an axial configuration with a 1,3-diaxial orientation to a C-3 methyl group. In the preferred transition state **2-85**, the *n*-butyl group at C-6 occupies an axial position. Both of these transition states have destabilizing interactions, and the result is modest selectivity (1.0:1.8 *cis:trans*) in the cyclization for **2-75***t*. Apparently, placing the *n*-butyl group axial is preferable to the diaxial interaction between the methyl groups in the transition state leading to **2-75***c*. The lowest energy chair conformer for each is product shown in Scheme 2-8.[40]

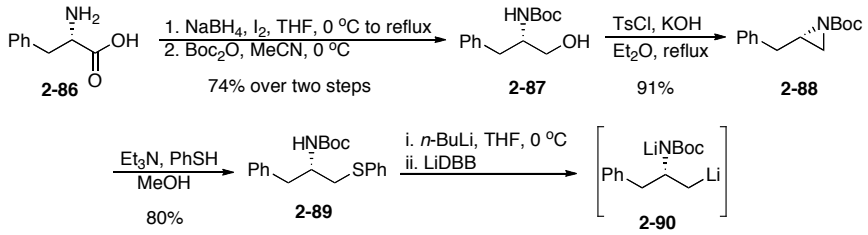
Scheme 2-8. The proposed chair-like transition states to explain the diastereoselectivity of THPO **2-74, 2-75*c*,** and **2-75*t***



Future Project: Development of β-Amino Alkyllithium Reagents

While exploring the functional group tolerance of the silyl enol ether Prins cyclization, a route to synthesize β-amino alkyllithium reagents was created (Table 2-3, entry 7). This route is currently being explored in the Rychnovsky lab because of the importance of chiral secondary amines in synthetic chemistry. The synthesis of the β-amino alkyllithium reagent began with the reduction and protection of L-phenylalanine to form amino alcohol **2-87** (Scheme 2-9). Activation of the alcohol moiety on **2-87** and treatment with base resulted in aziridine **2-88**. Ring opening with thiophenol afforded **2-89**. Deprotonation of the amine with *n*-butyllithium and single electron reduction of the carbon-sulfur bond with lithium di-*tert*-butylbiphenylide (LiDBB) furnished desired β-amino alkyllithium reagent **2-90**. This route occurs without loss of configuration at the stereogenic nitrogen center.

Scheme 2-9. Synthesis of a β-amino alkyllithium reagent **2-90**



The resulting β-amino alkyllithium reagent is enantioenriched and can be coupled to a variety of electrophiles, resulting in optically pure protected amines. A similar route has been explored by the Taylor group, however, only L-serine was investigated.[41] The Rychnovsky group will develop the scope of the method by starting from serveral different natural and unnatural α-amino acids to prepare the corresponding β-amino alkyllithium reagent. Coupling with electrophiles such as aldehydes, ketones, and Weinreb amides will produce enantioenriched amino alcohols or amino ketones.

Conclusion

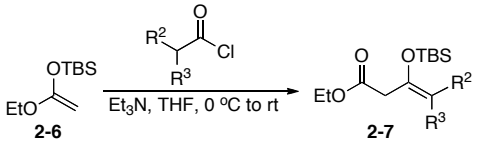
The silyl enol ether Prins reaction is highly diastereoselective with most substrates, and the major products are consistent with the cyclizations occurring through chair-like transition states. The reaction is tolerant of a variety of functional groups, and can form a quaternary center on the THPO with good diastereoselectivity. This method allows for the synthesis of substituted THPOs with substitution demonstrated at every on carbon atom in the ring. The flexibility of this silyl enol ether Prins method makes it a useful tool for synthesizing diverse THPO cores found in natural products or medicinal chemistry targets.

Experimental Section

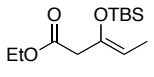
General Information. All air- and moisture-sensitive reactions were carried out in flame- or oven-dried flasks equipped with a magnetic stir bar under an argon atmosphere. All commercially available reagents were used as received unless stated otherwise. Tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, and dichloromethane (CH_2Cl_2), were passed through two 4 × 36 inch columns of anhydrous neutral alumina A-2 (8 × 14 mesh, LaRoche Chemicals; activated under a flow of Ar 350 °C for 12 h) to remove H_2O according to the procedure described by Grubbs.[42] Zinc dust was activated by sequential washing with 1 M HCl, water, and ethanol and was then dried under reduced pressure. $BF_3{\cdot}OEt_2$ was distilled neat under argon atmosphere. TMSOTf was distilled over CaH_2 under reduced pressure. Thin-layer chromatography (TLC) was performed on 250 μm layer silica gel plates, and developed plates were visualized by UV light, *p*-anisaldehyde, potassium permanganate, or vanillin.

^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra were recorded at 126 MHz. Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent, br. = broad), coupling constant(s) in Hertz (Hz), and integration. Infrared spectra were recorded on NaCl plates. High resolution mass spectrometry was performed using ESI-TOF. Structures not numbered in the article were numbered consecutively starting with **2-101**.

Procedures and Characterization

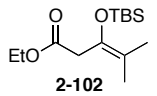


General Procedure to Form Ester 2-7. Triethylamine (1.7 equiv) was added dropwise to a solution of acid chloride (1.7 equiv) in THF (0.6 M relative to **2-6**) at 0 ºC. The mixture turned into a white sludge due to the formation of Et_3N•HCl salt. Silyl ketene acetal **2-6** (1.0 equiv) was added to the mixture and the solution was stirred overnight slowly warming from 0 ºC to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture extracted with Et_2O (3 x). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography of the crude residue produced ethyl ester **2-7**.



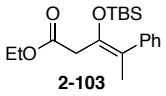
2-101

(*Z*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)pent-3-enoate (2-101). A sample of silyl ketene acetal **2-6** (2.50 g, 12.4 mmol) and propanoyl chloride (1.95 g, 21.1 mmol) was converted to **2-101** following the general procedure for ester **2-7** formation. Purification by column chromatography (5:1:94 Et_2O:Et_3N:hexanes) of the crude residue afforded **2-101** as a clear colorless oil (2.5 g, 77%): R_f = 0.49 (10% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (q, *J* = 6.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.02 (s 1H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 144.4, 106.4, 60.9, 43.0, 25.9, 18.4, 14.3, 11.19, –3.9; IR (thin film) 2958, 2931, 2859, 1742, 1682 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{13}H_{26}O_3SiNa$ $[M + Na]^+$ 281.1549, found 281.1542.



2-102

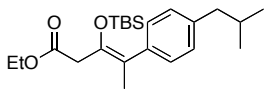
Ethyl 3-(tert-butyldimethylsilyloxy)-4-methylpent-3-enoate (2-102). 2-Bromo-2-methylpropionyl bromide (3.4 g, 15 mmol) was added dropwise to a suspension of activated zinc dust (1.9 g, 30 mmol) in THF (25 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then transferred via cannula to a solution of silyl ketene acetal **2-6** (1.0 g, 4.9 mmol) diluted with THF (25 mL) at 0 °C. The gray-green mixture was stirred for 14 h, slowly warming to room temperature. The reaction mixture was then diluted with Et_2O (25 mL) and washed with H_2O (15 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (5:1:94 Et_2O:Et_3N:hexanes) of the crude residue produced ethyl ester **2-102** as a colorless oil (0.81 g, 60%): R_f = 0.40 (5% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, J = 7.1 Hz, 2H), 3.15 (s, 2H), 1.64 (s, 3H), 1.62 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 137.6, 113.7, 60.8, 38.9, 26.0, 19.3, 18.4, 18.2, 14.5, –3.9; IR (thin film) 2931, 2858, 1739, 1682, 1473, 1257 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{14}H_{28}O_3SiNa$ $[M + Na]^+$ 295.1705, found 295.1703.



2-103

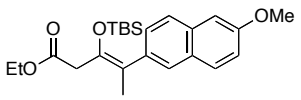
(*Z*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)-4-phenylpent-3-enoate (2-103). A sample of silyl ketene acetal **2-6** (300 mg, 1.48 mmol) and 2-phenylpropanoyl (424 mg, 2.52 mmol) was converted to **2-103** following the general procedure for ester **2-7** formation. Purification by column chromatography (5:1:94 Et_2O:Et_3N:hexanes) of the crude residue afforded **2-103** as a clear colorless oil (400 mg, 81%): R_f = 0.43 (5% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.31–7.25 (m, 4H), 7.15 (t, J = 7.5 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.29 (s, 2H), 1.96 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.73 (s, 9H), –0.25 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 141.9, 139.8, 129.4, 127.9, 126.1, 118.1, 60.9, 39.8, 25.7, 19.6, 18.1, 14.4, –4.5; IR (thin film) 2956, 2930, 2896, 2858, 1738, 1660 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{19}H_{30}O_3SiNa$ [M + Na]$^+$ 357.1862, found 357.1863.



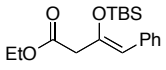
2-104

(*Z*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)-4-(4-isobutylphenyl)pent-3-enoate (2-104). A sample of silyl ketene acetal **2-6** (267 mg, 1.32 mmol) and 2-(4-isobutylphenyl)propanoyl chloride (504 mg, 2.24 mmol) was converted to **2-104** following the general procedure for ester **2-7** formation. Purification by column chromatography (15:1:84 EtOAc:Et_3N:hexanes) of the crude residue afforded **2-104** as a clear colorless oil (362 mg, 70%): R_f = 0.67 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 10.5 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.28 (s, 2H), 2.44 (d, J = 7.5 Hz, 2H), 1.95 (s, 3H), 1.84 (app. septet, J = 6.8 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.89 (d, J = 7.0 Hz, 6H), 0.73 (s, 9H), –0.25 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 139.8, 139.7, 139.4, 129.3, 128.9, 118.3, 61.1, 45.6, 40.1, 30.7, 26.0, 22.7, 19.9, 18.4, 14.6, –4.2; IR (thin film) 2955, 2929, 2093, 2858, 1741, 1658 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{23}H_{38}O_3SiNa$ [M + Na]$^+$ 413.2488, found 413.2486.



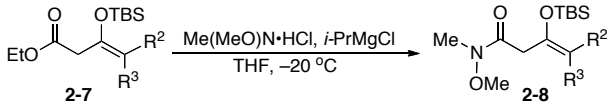
2-105

(*Z*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)-4-(6-methoxynaphthalen-2-yl)pent-3-enoate (2-105). Triethylamine (0.31 mL, 2.22 mmol) was added dropwise to a solution of 2-(6-methoxynaphthalen-2-yl)propanoyl chloride (552 mg, 2.22 mmol) in THF (0.6 M relative to **2-6**) at 0 ºC. The mixture turned into a white sludge due to the formation of $Et_3N{\cdot}HCl$ salt. Silyl ketene acetal **2-6** (264 mg, 1.30 mmol) was added to the mixture and the solution was stirred overnight slowly warming from 0 ºC to room temperature. A second portion of triethylamine (0.31 mL, 2.22 mmol) was added dropwise to the solution at rt. The reaction was monitored by TLC and once starting material was consumed, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded **2-105** as a clear colorless oil (471 mg, 87%): R_f = 0.7 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (br. s, 1H), 7.65 (dd, *J* = 9.0, 7.0 Hz, 2H), 7.44 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.11–7.09 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 3.34 (s, 2H), 2.04 (s, 3H), 1.32 (t, *J* = 7.25 Hz, 3H), 0.71 (s, 9H), –0.30 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 157.7, 140.3, 137.3, 133.4, 129.7, 129.1, 128.8, 127.9, 126.3, 118.8, 118.1, 105.9, 61.2, 55.6, 40.2, 26.0, 19.8, 18.3, 14.7, –4.2; IR (thin film) 2931, 2956, 2897, 2857, 1739, 1605 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{24}H_{34}O_4SiNa$ $[M + Na]^+$ 437.2124, found 437.2112.



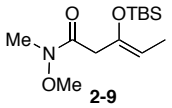
2-106

(*Z*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)-4-phenylbut-3-enoate (2-106). A sample of silyl ketene acetal **2-6** (200 mg, 1.00 mmol) and phenylacetyl chloride (260 mg, 1.68 mmol) was converted to **2-106** following the general procedure for ester **2-7** formation. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded **2-106** as a clear colorless oil (98 mg, 31%): R_f = 0.65 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 2H), 7.25 (app. t, *J* = 7.8 Hz, 2H), 7.13 (app. t, *J* = 7.5 Hz, 1H), 5.58 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.2 (s, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 145.5, 136.0, 128.7, 127.9, 126.0, 111.6, 61.0, 43.8, 25.8, 18.3, 14.3, –3.8; IR (thin film) 2931, 2858, 1740, 1654 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{28}O_3SiNa$ $[M + Na]^+$ 343.1705, found 343.1712.



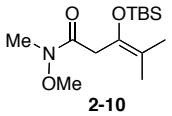
2-7 **2-8**

General Procedure to Form Weinreb Amide 2-8.[21] A solution of 2.0 M *i*-PrMgCl (2.4 equiv) in THF was added dropwise to a solution of ethyl ester **2-7** (1.0 equiv) and Me(MeO)NH•HCl (1.2 equiv) in THF (0.12 M relative to **2-7**) at –20 °C. The mixture was stirred at –20 °C for 2 h and the reaction was then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (3 x). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography of the crude residue afforded Weinreb amide **2-8**.



2-9

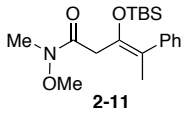
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methylpent-3-enamide (2-9). A sample of 258 mg of ester **2-101** (1.0 mmol) was converted to **2-9** following the general procedure for Weinreb amide **2-8** formation; the combined organic layers were dried over anhydrous Na_2SO_4 instead of $MgSO_4$. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded **2-9** as a clear colorless oil (230 mg, 84%): R_f = 0.47 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (q, *J* = 6.8 Hz, 1H), 3.61 (s, 3H), 3.11 (app. s, 5H), 1.49 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 144.7, 105.0, 61.2, 40.3, 32.2, 25.7, 18.18, 10.9, –4.1; IR (thin film) 2957, 2931, 2896, 2858, 1682 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{13}H_{27}NO_3SiNa$ $[M + Na]^+$ 296.1658, found 296.1663.



2-10

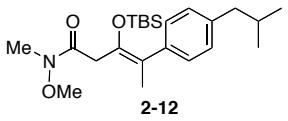
3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,4-dimethylpent-3-enamide (2-10). A sample of 140 mg of ester **2-102** (0.51 mmol) was converted to **2-10** following the general procedure for Weinreb amide **2-8** formation. Purification by column chromatography (30:1:69 Et_2O:Et_3N:hexanes) of the crude residue afforded Weinreb amide **2-10** as a colorless oil (0.12 g, 83%): R_f = 0.28 (30% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.30 (s, 2H), 3.17 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 137.9, 113.3, 61.3, 37.0, 32.6, 26.0, 19.2, 18.4, 18.2, –3.9; IR (thin film) 2931, 2858,

1678, 1462, 1254 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{14}H_{29}NO_3SiNa$ $[M + Na]^+$ 310.1814, found 310.1819.



2-11

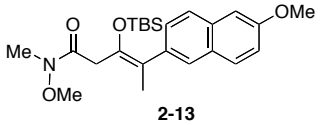
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-4-phenylpent-3-enamide (2-11). A sample of 843 mg of ester **2-103** (2.50 mmol) was converted to **2-11** following the general procedure for Weinreb amide **2-8** formation. The amount of the 2.0 M *i*-PrMgCl solution added was increased from 2.4 equiv to 3.0 equiv. The amount of Me(MeO)NH•HCl added was increased from 1.2 equiv to 1.5 equiv. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded **2-11** as a clear colorless oil (733 mg, 83%): R_f = 0.42 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 3.75 (s, 3H), 3.44 (s, 2H), 3.22 (s, 3H), 1.96 (s, 3H), 0.73 (s, 9H), –0.24 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 142.1, 140.3, 129.4, 127.8, 126.0, 117.8, 61.4, 38.2, 32.6, 25.8, 19.4, 18.1, –4.4; IR (thin film) 2955, 2930, 2895, 2857, 1682 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{19}H_{31}NO_3SiNa$ $[M + Na]^+$ 372.1971, found 372.1963.



2-12

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-4-(4-isobutylphenyl)-*N*-methoxy-*N*-methylpent-3-enamide (2-12). A solution of 2.0 M *i*-PrMgCl (0.30 mL, 0.60 mmol) in THF was added dropwise to a two neck flask containing ethyl ester **2-104** (116 mg, 0.30 mmol) and Me(MeO)NH•HCl (29 mg, 0.30 mmol) in THF (1.25 mL) and toluene (1.25 mL) at rt. The mixture was stirred for 6 h at rt. Four portions of 2.0 M *i*-PrMgCl (each portion: 0.30 mL, 0.60

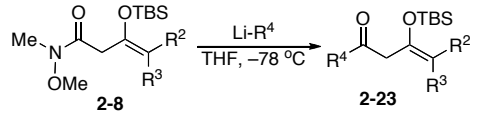
mmol) in THF and Me(MeO)NH•HCl (each portion: 29 mg, 0.30 mmol) were added to the solution at rt in six hour intervals. The reaction was monitored by TLC and once starting material was consumed, the reaction was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with Et_2O (3 x 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography (15:1:84 EtOAc:Et_3N:hexanes) of the crude residue afforded Weinreb amide **2-12** as a clear colorless oil (92 mg. 76%): R_f = 0.17 (15 % EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 3.74 (s, 3H), 3.43 (s, 2H), 3.22 (s, 3H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.94 (s, 3H), 1.83 (app. septet, *J* = 6.7 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.73 (s, 9H), –0.24 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 140.0, 139.4 (2), 129.1, 128.6, 117.7, 61.4, 45.3, 38.3, 32.6, 30.4, 25.9, 22.4, 19.5, 18.1, –4.4; IR (thin film) 2954, 2930, 2857, 1677 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{23}H_{39}NO_3SiNa$ $[M + Na]^+$ 428.2597, found 428.2599.



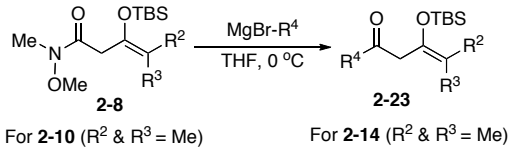
2-13

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-4-(6-methoxynaphthalen-2-yl)-*N*-methylpent-3-enamide (2-13). A solution of 2.0 M *i*-PrMgCl (0.48 mL, 0.96 mmol) in THF was added dropwise to a two neck flask containing ethyl ester **2-105** (200 mg, 0.48 mmol) and Me(MeO)NH•HCl (47 mg, 0.48 mmol) in THF (2 mL) and toluene (2 mL) at 0 ºC. The mixture was stirred for 7 h slowly warming to rt. A second portion of 2.0 M *i*-PrMgCl (0.48 mL, 0.96 mmol) in THF and Me(MeO)NH•HCl (47 mg, 0.48 mmol) was added to the solution and stirred overnight at rt. A third portion of 2.0 M *i*-PrMgCl (0.48 mL, 0.96 mmol) in THF and

Me(MeO)NH•HCl (47 mg, 0.48 mmol) was added to the solution. The reaction was monitored by TLC and once starting material was consumed, the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with EtOAc (5 x 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded Weinreb amide **2-13** as a clear colorless oil (183 mg. 90%): R_f = 0.55 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (br. s, 1H), 7.65 (app. dd, *J* = 8.8, 6.1 Hz, 2H), 7.5 (app. d, *J* = 8.5 Hz, 1H), 7.12–7.07 (m, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 3.49 (s, 2H), 3.24 (s, 3H), 2.04 (s, 3H), 0.72 (s, 9H), 0.29 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 157.3, 140.5, 137.2, 133.0, 129.4, 128.8, 128.6, 127.7, 126.0, 118.5, 117.6, 105.6, 77.4, 61.4, 55.3, 38.2, 25.8, 19.4, 18.1, –4.3; IR (thin film) 2954, 2932, 2856, 2896, 1674, 1604 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{24}H_{35}NO_4SiNa$ $[M + Na]^+$ 452.2233, found 452.2219.

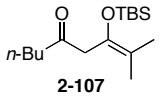


General Procedure to Form Ketone 2-14/2-23 with an Organolithium Reagent. To a flask containing Weinreb amide **2-8/2-10** (1.0 equiv) and THF (0.3 M) was added an organolithium reagent (1.5 equiv) dropwise at –78 °C. The mixture was stirred for 5 h at –78 °C, and the reaction was quenched with saturated aqueous NH_4Cl. The solution was extracted with CH_2Cl_2 (4 x). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography of the crude residue afforded ketone **2-14/2-23**.



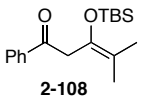
For **2-10** (R^2 & R^3 = Me) For **2-14** (R^2 & R^3 = Me)

General Procedure to Form Ketone 2-14/2-23 with a Grignard Reagent. A Grignard reagent (1.5 equiv) was added dropwise to a solution of Weinreb amide **2-8/2-10** (1.0 equiv) in THF (0.3 M) at 0 ºC. The mixture was stirred overnight, slowly warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (4 x). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography of the crude residue afforded ketone **2-14/2-23**.



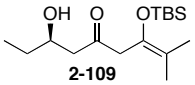
2-107

3-(*tert*-Butyldimethylsilyloxy)-2-methylnon-2-en-5-one (2-107). *n*BuLi (2.27 M in hexanes, 2.30 mL) and Weinreb amide **2-10** (1.00 g, 3.51 mmol) was were converted to ketone **2-107** following the general procedure for ketone **2-14** formation with an organlithium reagent. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-107** as a clear yellow oil (0.81 g, 82%): R_f = 0.72 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (s, 2H), 2.44 (t, J = 7.4 Hz, 2H), 1.65 (s, 3H), 1.61 (s, 3H), 1.56–1.50 (m, 2H), 1.32–1.27 (m, 2H), 0.92 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.6, 138.3, 113.8, 47.8, 40.8, 25.95, 25.91, 22.4, 19.4, 18.3, 18.2, 14.0, –3.8; IR (thin film) 2958, 2931, 2859, 1715 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{16}H_{32}O_2SiNa$ $[M + Na]^+$ 307.2069, found 307.2073.



2-108

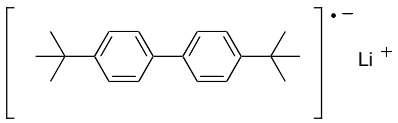
3-(*tert*-Butyldimethylsilyloxy)-4-methyl-1-phenylpent-3-en-1-one (2-108). Freshly prepared PhMgBr (0.83 M in THF, 1.25 mL) and Weinreb amide **2-10** (200 mg, 0.70 mmol) were converted to ketone **2-108** following the general procedure for ketone **2-14** formation with a Grignard reagent. Purification by column chromatography (5:1:94 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-108** as a colorless oil (155 mg, 73%): R_f = 0.51 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.54 (app. t, *J* = 7.4 Hz, 1H), 7.44 (app. t, *J* = 7.7 Hz, 2H), 3.80 (s, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 137.8, 137.0, 133.0, 128.6, 128.2, 113.9, 43.8, 25.9, 19.3, 18.3, 18.2, –3.9; IR (thin film) 3062, 2929, 2857, 1682 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{28}O_2SiNa$ $[M + Na]^+$ 327.1756, found 327.1754.



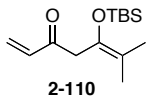
2-109

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-2-methylnon-2-en-5-one (2-109). In a two neck round-bottom flask equipped with a glass stir bar, a crystal of indicator 1,10-phenanthroline, *β*-thiophenyl alcohol **2-54** (3.8 g, 21 mmol), and THF (41 mL) were cooled to –78 °C. The reaction mixture was titrated with 2.6 M *n*-butyllithium (8.0 mL, 21 mmol) in hexanes until a dark red-brown color persisted. A solution of nominally 0.4 M LiDBB (40 mmol) in THF was added portion wise until a green-blue color persisted for 10 min (see below for LiDBB synthesis). When the reaction turned an orange-brown color, Weinreb amide **2-10** was added dropwise at –78 °C. The mixture was stirred for 22 h at –78 °C, then warmed to 0 °C, and the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The reaction mixture was

extracted with Et_2O (4 x 100 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (50:45:5 hexanes:CH_2Cl_2:EtOAc) of the crude residue produced ketone **2-109** as a clear yellow oil (1.71 g, 82%): R_f = 0.31 (50:45:5 hexanes:CH_2Cl_2:EtOAc); $[\alpha]^{24}_D$ = –29.9 (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01–3.88 (m, 1H), 3.19 (s, 2H), 3.05 (d, *J* = 2.9 Hz, 1H), 2.68 (dd, *J* = 17.7, 2.6 Hz, 1H), 2.53 (dd, *J* = 17.7, 9.2 Hz, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 1.61–1.38 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 137.7, 114.5, 69.3, 48.4, 47.0, 29.4, 26.0, 19.4, 18.3, 18.2, 10.0, –3.8; IR (thin film) 3444, 2962, 2862, 1712, 1678, 1462, 1254 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{16}H_{32}O_3SiNa$ $[M + Na]^+$ 323.2018, found 323.2010.

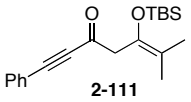


Lithium di-*tert*-butylbiphenylide. In a two neck round-bottom flask equipped with a glass stir bar, 4,4'-di-*tert*-butylbiphenyl (0.99 g, 3.7 mmol) was heated with a torch *in vacuo* until sublimation occured. The flask was purged with argon and one crystal of indicator 1,10-phenanthroline was added under positive argon pressure. Dry THF (7.4 mL) was added and the solution was cooled to 0 °C. The reaction mixture was titrated with *n*-butyllithium (2.2 M in hexanes) until a dark red-brown color persisted to remove any trace H_2O. Lithium metal (180 mg, 26.0 mmol) was rinsed with hexanes and cut into the reaction flask. The solution turned dark green after 20 s and the reaction mixture was stirred for 5 h at 0 °C. The LiDBB (nominally 0.4 M) was used directly in the next reaction.



2-110

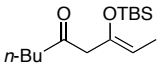
5-(*tert*-Butyldimethylsilyloxy)-6-methylhepta-1,5-dien-3-one (2-110). Vinylmagnesium bromide (0.87 M in THF, 1.7 mL) and Weinreb amide **2-10** (100 mg, 0.348 mmol) were converted to ketone **2-110** following the general procedure for ketone **2-14** formation with a Grignard reagent. The solution was stirred for 3 h slowly warming to room temperature. The mixture was extracted with CH_2Cl_2 (3 x 5 mL) instead of EtOAc. Purification by column chromatography (100% hexanes on florisil instead of Si_2O) of the crude residue afforded ketone **2-110** as a yellow oil (60 mg, 67%): R_f = 0.43 (100% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.27 (dd, *J* = 17.5, 1.4 Hz, 1H), 5.73 (dd, *J* = 10.6, 1.4 Hz, 1H), 3.34, (s, 2H), 1.65 (s, 3H), 1.60 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 137.6, 135.0, 128.3, 114.2, 45.8, 25.9, 19.2, 18.3, 18.2, –3.8; IR (thin film) 2957, 2930, 2858, 1698, 1678, 1617 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{14}H_{26}O_2SiNa$ [M + Na]$^+$ 277.1600, found 277.1607.



2-111

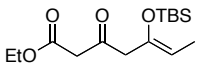
5-(*tert*-Butyldimethylsilyloxy)-6-methyl-1-phenylhept-5-en-1-yn-3-one (2-111). *n*-BuLi (2.27 M in hexanes, 0.22 mL) was added to a solution of phenyl acetylene (57 μL, 0.52 mmol) in THF (1.2 mL) at –78 ºC. The mixture was stirred for 1 h then Weinreb amide **2-10** (100 mg, 0.35 mmol) was added. The solution was stirred for 4 h slowly warming to rt. The reaction was quenched with saturated aqueous NH_4Cl (2 mL), and the mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:19 EtOAc:hexanes) of the

crude residue afforded ketone **2-111** as a yellow oil (45 mg, 39%): R_f = 0.62 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.45–7.43 (m, 1H), 7.40–7.36 (m, 2H), 3.46 (s, 2H), 1.72 (s, 3H), 1.71 (s, 3H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.8, 137.1, 133.3, 130.8, 128.7, 120.3, 115.0, 91.2, 88.0, 49.5, 30.0, 19.6, 18.4, 18.3, –3.7; IR (thin film) 2957, 2929, 2858, 1667 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{20}H_{28}O_2SiNa$ [M + Na]$^+$ 351.1756, found 351.1754.



2-112

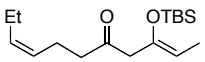
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)non-2-en-5-one (2-112). Weinreb amide **2-9** (200 mg, 0.82 mmol) and *n*-BuLi (2.27 M in hexanes, 0.38 mL) were converted to ketone **2-112** following the general procedure for ketone **2-23** formation with an organolithium reagent. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-112** as a clear colorless oil (130 mg, 66%): R_f = 0.66 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (q, *J* = 6.7 Hz, 1H), 3.03 (s, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.56–1.51 (m, 2H), 1.26 (app. sextet, *J* = 7.4 Hz, 2H), 0.93 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 145.3, 107.0, 51.7, 40.9, 25.89, 25.86, 22.4, 18.3, 14.0, 11.2, –3.9; IR (thin film) 2958, 2932, 2860, 1716, 1674 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{30}O_2SiNa$ [M + Na]$^+$ 293.1913, found 293.1909.



2-113

(*Z*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-3-oxohept-5-enoate (2-113). Ethyl acetate (0.09 mL, 0.88 mmol) was added dropwise to a freshly made solution of LDA (0.5 M in THF, 1.8 mL) over

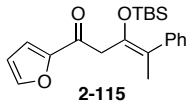
5 min at –78 ºC. The mixture was stirred for 1 h. DMPU (0.13 mL, 1.10 mmol) and Weinreb amide **2-9** (200 mg, 0.82 mmol) were added to the solution, and the mixture was stirred for 28 h at –78 ºC. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-113** as a clear colorless oil (129 mg, 59%): R_f = 0.44 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (q, *J* = 6.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 3.18 (s, 2H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.0, 167.6, 144.4, 108.3, 61.4, 51.8, 47.5, 25.8, 18.3, 14.2, 11.3, –3.9; IR (thin film) 2932, 2957, 2859, 2897, 1748, 1721, 1676 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{28}O_4SiNa$ [M + Na]$^+$ 323.1655, found 323.1652.



2-114

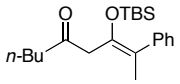
(2*Z*,8*Z*)-3-(*tert*-Butyldimethylsilyloxy)undeca-2,8-dien-5-one (2-114). Freshly formed (*Z*)-hex-3-enylmagnesium bromide (1.0 M in THF, 2.0 mL) and amide **2-9** (365 mg, 1.30 mmol) were converted to ketone **2-114** following the general procedure for ketone **2-23** formation with a Grignard reagent. The mixture was stirred for 6 h at 0 ºC, and the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was dried with anhydrous $MgSO_4$ instead of Na_2SO_4. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-114** as a colorless oil (289 mg, 75%): R_f = 0.68 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40–5.36 (m, 1H), 5.30–5.25 (m, 1H), 4.65 (q, *J* = 6.7 Hz, 1H), 3.04 (s, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.28 (q, *J* = 7.4 Hz, 2H), 2.04 (quintet, *J* = 7.3 Hz, 2H),

1.57 (d, J = 6.7 Hz, 3H), 0.95 (t, J = 1.0 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.2, 145.2, 132.8, 127.5, 107.2, 51.8, 41.2, 25.9, 21.6, 20.6, 18.3, 14.4, 11.2, –3.8; IR (thin film) 3007, 2988, 2959, 2859, 2896, 1718, 1675 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{17}H_{32}O_2SiNa$ [M + Na]$^+$ 319.2069, found 319.2063.



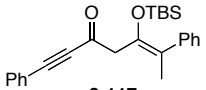
2-115

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-1-(furan-2-yl)-4-phenylpent-3-en-1-one (2-115). *n*-BuLi (2.27 M in hexanes, 0.18 mL) was added to a solution of furan (30 μL, 0.40 mmol) and TMEDA (60 μL, 0.40 mmol) in THF (0.95 mL) at 0 ºC. The mixture was stirred for 1 h followed by addition of Weinreb amide **2-11** (100 mg, 0.29 mmol). The solution was stirred for 1 h, and then the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (15:1:84 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-115** as a yellow oil (89 mg, 87%): R_f = 0.52 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, J = 1.65, 0.69 Hz, 1H), 7.33 (dd, J = 3.5, 0.7 Hz, 1H), 7.31–7.24 (m, 4H), 7.15 (tt, J = 7.1, 2.2 Hz, 1H), 6.56 (dd, J = 3.6, 1.7 Hz, 1H), 3.78 (s, 2H), 1.99 (s, 3H), 0.70 (s, 9H), –0.26 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.3, 152.6, 146.4, 141.8, 140.0, 129.4, 127.9, 126.2, 118.7, 117.4, 112.4, 44.7, 25.8, 19.6, 18.1, –4.4; IR (thin film) 3022, 2954, 2928, 2894, 2856, 1682 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{21}H_{28}O_3SiNa$ [M+ Na]$^+$ 379.1705, found 379.1696.



2-116

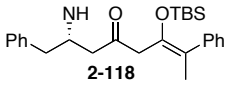
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-phenylnon-2-en-5-one (2-116). Weinreb amide **2-11** (438 mg, 1.25 mmol) and *n*-BuLi (2.27 M in hexanes, 0.83 mL) were converted to ketone **2-116** following the general procedure for ketone **2-23** formation with an organolithium reagent. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-116** as a light yellow oil (337 mg, 78%): R_f = 0.68 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.25 (m, 4H), 7.19–7.15 (m, 1H), 3.29 (s, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 1.96 (s, 3H), 1.64–1.58 (m, 2H), 1.39–1.32 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.72 (s, 9H), –0.27 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.0, 141.8, 140.6, 129.2, 128.0, 126.2, 118.5, 48.8, 40.9, 25.9, 25.7, 22.5, 19.6, 18.0, 14.0, –4.4; IR (thin film) 2956, 2930, 2858, 1716, 1652 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{21}H_{34}O_2SiNa$ $[M+Na]^+$ 369.2226, found 369.2233.



2-117

(*Z*)-5-(*tert*-Butyldimethylsilyloxy)-1,6-diphenylhept-5-en-1-yn-3-one (2-117). *n*-BuLi (2.27 M in hexanes, 0.28 mL) was added to a solution of phenyl acetylene (70 μL, 0.63 mmol) in THF (1.9 mL) at –78 ºC. The mixture was stirred for 1.5 h then Weinreb amide **2-11** (200 mg, 0.57 mmol) was added. The solution was stirred for 2.5 h at –78 ºC, warmed to 0 ºC, and stirred for an additional 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column

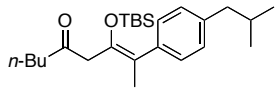
chromatography (15:1:84 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-117** as a yellow oil (130 mg, 58%): R_f = 0.76 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.47–7.44 (m, 1H), 7.39–7.34 (m, 4H), 7.28 (app. t, *J* = 8.3 Hz, 2H), 7.19–7.16 (m, 1H), 3.56 (s, 2H), 2.07 (s, 3H), 0.73 (s, 9H), –0.23 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4, 141.8, 139.5, 133.3, 130.9, 129.3, 128.8, 128.0, 126.3, 120.2, 120.0, 91.4, 87.9, 50.3, 25.7, 19.9, 18.1, –4.4; IR (thin film) 2954, 2928, 2856, 1673 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{25}H_{30}O_2SiNa$ $[M + Na]^+$ 413.1913, found 413.1923.



2-118

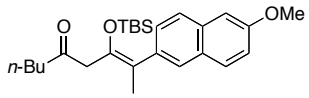
(*S*,*Z*)-*tert*-Butyl 6-(tert-butyldimethylsilyloxy)-4-oxo-1,7-diphenyloct-6-en-2-ylcarbamate (2-118). In a two neck round-bottom flask equipped with a glass stir bar, a crystal of indicator 1,10-phenanthroline, *β*-thiophenyl amine **2-89** (300 mg, 0.86 mmol), and THF (5.4 mL) were cooled to –78 °C. The reaction mixture was titrated with *n*-butyllithium (0.38 mL, 0.86 mmol, 2.27 M in hexanes) until a dark red-brown color persisted. A solution of nominally 0.4 M LiDBB (1.7 mmol) in THF was added portion wise until a green-blue color persisted for 10 min. When the reaction turned an orange-brown color, Weinreb amide **2-11** was added dropwise at –78 °C. The mixture was stirred for 22 h at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue produced ketone **2-118** as a clear yellow oil (120 mg, 85%): R_f = 0.5 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = –7.2 (*c* 1.75, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.29–7.14 (m, 10H); 5.12 (br. s, 1H), 4.22–4.17 (m, 1H), 3.30–3.23 (m, 2H), 3.02–2.73 (m, 4H), 1.91 (s, 3H), 1.40 (s, 9H), 0.68

(s, 9H), –0.29 (d, J = 5.8 Hz, 6H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.9, 155.4, 141.4, 140.0, 138.3, 129.4, 129.2, 128.6, 127.9, 126.6, 126.3, 119.0, 79.3, 49.1, 48.5, 43.5, 40.4, 28.4, 25.7, 19.6, 18.0, –4.5; IR (thin film) 3438, 3358, 3060, 3027, 2929, 2858, 1722, 1713, 1694, 1682 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{31}H_{45}NO_4SiNa$ [M + Na]$^+$ 546.3016, found 546.3005.



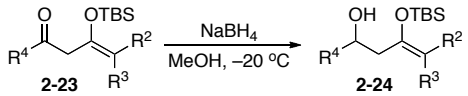
2-119

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(4-isobutylphenyl)non-2-en-5-one (2-119). Weinreb amide **2-12** (176 mg, 0.43 mmol) and *n*-BuLi (2.49 M in hexanes, 0.36 mL) were converted to ketone **2-119** following the general procedure for ketone **2-23** formation with an organolithium reagent. The mixture was stirred overnight slowly warming from –78 ºC to 0 ºC. The solution was extracted with EtOAc instead of CH_2Cl_2. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-119** as a clear colorless oil (126 mg, 73%): R_f = 0.86 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 3.28 (s, 2H), 2.61 (t, J = 7.4 Hz, 2H), 2.44 (d, J = 7.1 Hz, 2H), 1.96 (s, 3H), 1.84 (app. septet, J = 6.9 Hz, 1H), 1.61 (app. quintet, J = 7.4 Hz, 2H), 1.35 (app. sextet, J = 7.4 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6 H), 0.72 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.2, 140.3, 139.6, 139.0, 128.9, 128.7, 118.4, 48.8, 45.3, 40.8, 30.4, 25.9, 25.8, 22.5, 22.4, 19.7, 18.0, 14.0, –4.4; IR (thin film) 2957, 2930, 2859, 1717, 1653 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{25}H_{42}O_2SiNa$ [M+ Na]$^+$ 425.2852, found 425.2842.



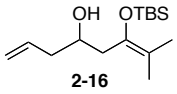
2-120

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(6-methoxynaphthalen-2-yl)non-2-en-5-one (2-120). Weinreb amide **2-13** (50 mg, 0.12 mmol) and *n*-BuLi (2.37 M in hexanes, 0.16 mL) were converted to ketone **2-120** following the general procedure for ketone **2-23** formation with an organolithium reagent. *n*-BuLi was added in two equal portions; the second portion was added after 5 h. The mixture was stirred for an additional 1 h. The solution was extracted with EtOAc instead of CH_2Cl_2. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **2-120** as a clear colorless oil (30 mg, 60%): R_f = 0.63 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.4 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.7 Hz, 2H), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.13–7.09 (m, 2H), 3.92 (s, 3H), 3.35 (s, 2H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.04 (s, 3H), 1.65 (app. quintet, *J* = 7.5 Hz, 2H), 1.39 (app. sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 3H), 0.70 (s, 9H), –0.32 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.9, 157.5, 140.8, 136.9, 133.2, 129.4, 128.9, 128.4, 127.6, 126.2, 118.7, 118.3, 105.7, 55.4, 49.0, 41.0, 26.0, 25.8, 22.6, 19.7, 18.0, 14.0, –4.3; IR (thin film) 2956, 2931, 2858, 1717, 1633, 1605 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{26}H_{38}O_3SiNa$ $[M + Na]^+$ 449.2488, found 449.2477.



General Procedure to Form Alcohol 2-15/2-24. Sodium borohydride (1.1 equiv) was added to a vial containing ketone **2-14/2-23** (1.0 equiv) in MeOH (0.2 M relative to the ketone) at –20 °C. The reaction was monitored by TLC and when starting material was consumed, the reaction was

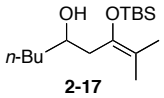
quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc (3 x) and the organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography of the crude residue afforded alcohol **2-15/2-24**.



2-16

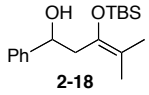
6-(*tert*-Butyldimethylsilyloxy)-7-methylocta-1,6-dien-4-ol (2-16). Allyl magnesium bromide (1.0 M in Et_2O, 1.05 mL) was added dropwise to a solution of Weinreb amide **2-10** (200 mg, 0.70 mmol) and THF (2.3 mL) at 0 ºC. The gray mixture was stirred overnight, slowly warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (4 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was diluted with CH_2Cl_2 (3.4 mL) and DIBAL-H (1.2 M in toluene, 1.13 mL) was added dropwise at –78 ºC over 10 min. The mixture was stirred for 50 min at –78 ºC then warmed to 0 ºC. Immediately after warming, 5.0 mL aqueous Rochelle salt (0.1 M) was added slowly and the mixture was stirred for another 1 h. The solution was extracted with CH_2Cl_2 (4 x 20 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-16** as a clear colorless oil (86 mg, 47%): R_f = 0.53 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87–5.82 (m, 1H), 5.13–5.08 (m, 2H), 3.88–3.84 (m, 1H), 2.33–2.19 (m, 5H), 1.63 (s, 3H), 1.62 (s, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 135.2, 117.6, 113.1, 69.7, 41.3, 39.2, 26.0, 19.3, 18.4, 18.3, –3.70, –3.73; IR (thin film) 3417,

3077, 2957, 2929, 2859, 1680, 1642 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{30}O_2SiNa$ $[M + Na]^+$ 293.1913, found 293.1909.



2-17

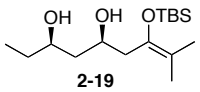
3-(*tert*-Butyldimethylsilyloxy)-2-methylnon-2-en-5-ol (2-17). Sodium borohydride (118 mg, 3.12 mmol) was added to a vial containing ketone **2-107** (810 mg, 0.78 mmol) in 14 mL MeOH at –20 ºC. The mixture was stirred for 1 h at –20 ºC and the reaction was quenched with H_2O (30 mL). The solution was extracted with EtOAc (3 x 50 mL) and the organic layers were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-17** as a clear light yellow oil (745 mg, 92%): R_f = 0.40 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82–3.77 (m, 1H), 2.30–2.20 (m, 2H), 2.09 (br. s, 1H), 1.633 (s, 3H), 1.628 (s, 3H), 1.50–1.31 (m, 6H), 0.94 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.11 (d, *J* = 9.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8, 113.1, 70.4, 39.9, 36.7, 28.1, 26.0, 22.9, 19.3, 18.4, 18.3, 14.2, –3.7; IR (thin film) 3388, 2957, 2930, 2859, 1678 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{16}H_{34}O_2SiNa$ $[M + Na]^+$ 309.2226, found 309.2228.



2-18

3-(*tert*-Butyldimethylsilyloxy)-4-methyl-1-phenylpent-3-en-1-ol (2-18). Ketone **2-108** (237 mg, 0.78 mmol) was converted to alcohol **2-108** following the general procedure for alcohol **2-15** formation. The mixture was stirred overnight, slowly warming to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ instead of NH_4Cl and the mixture was

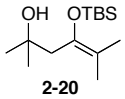
dried with anhydrous Na_2SO_4 instead of $MgSO_4$. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-18** as a clear colorless oil (203 mg, 85%): R_f = 0.47 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (m, 4H), 7.27–7.25 (m, 1H), 4.91 (ddd, *J* = 9.3, 3.7, 2.1 Hz, 1H), 2.60 (d, *J* = 2.1 Hz, 1H), 2.57 (dd, *J* = 8.5, 4.8 Hz, 1H), 2.44 (dd, *J* = 14.1, 3.7 Hz, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 0.99 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 141.1, 128.4, 127.4, 125.8, 114.0, 72.7, 42.6, 26.1, 19.1, 18.4, 18.3, –3.6, –3.7; IR (thin film) 3420, 3063, 2956, 2929, 2858, 1681 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{30}O_2SiNa$ [M + Na]$^+$ 329.1913, found 329.1910.



2-19

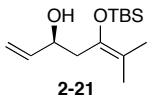
(3*R*,5*R*)-7-(*tert*-Butyldimethylsilyloxy)-8-methylnon-7-ene-3,5-diol (2-19). A solution of 1.0 M Et_2BOMe (0.92 mL, 0.92 mmol) in THF was added dropwise to a solution of ketone **2-109** (250 mg, 0.83 mmol) in THF (13 mL) and MeOH (25 mL) at –78 °C. After 30 min, $NaBH_4$ (35 mg, 0.92 mmol) was added and the reaction mixture was stirred for 4 h at –78 °C. Acetic acid (0.53 mL, 9.3 mmol) was added dropwise and the solution was warmed to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The crude product was extracted with EtOAc (6 x 15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was diluted with methanol, stirred for 15 h at room temperature, and concentrated under reduced pressure in order to remove bound Et_2BOMe. The crude residue was diluted again with MeOH, stirred for another 2 h at room temperature, and concentrated to remove residual bound Et_2BOMe. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue produced diol **2-19** as a clear colorless oil (200 mg, 80%):

R_f = 0.23 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = –4.2 (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dtd, *J* = 12.5, 4.6, 2.4 Hz, 1H), 3.82–3.75 (m, 1H), 3.44 (br s, 1H), 2.89 (br s, 1H), 2.35 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.24 (dd, *J* = 14.1, 4.6 Hz, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 1.60–1.56 (m, 1H), 1.54–1.45 (m, 3H), 0.95 (s, 9H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 113.5, 74.0, 72.0, 42.3, 40.5, 30.7, 26.0, 19.3, 18.4, 18.3, 9.8, –3.69, –3.74; IR (thin film) 3356, 2931, 2858, 1678, 1462, 1257 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{16}H_{34}O_3SiNa$ $[M + Na]^+$ 325.2175, found 325.2176.



2-20

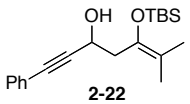
4-(*tert*-Butyldimethylsilyloxy)-2,5-dimethylhex-4-en-2-ol (2-20). Methylmagnesium bromide (3.0 M in Et_2O, 1.0 mL) was added dropwise to a solution of ester **2-7** (330 mg, 1.2 mmol) in 6 mL of Et_2O at 0 ºC. The mixture was stirred overnight, warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-20** as a clear colorless oil (204 mg, 66%): R_f = 0.41 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (s, 1H), 2.30 (s, 2H), 1.63 (s, 3H), 1.62, (s, 3H), 1.21 (s, 6H), 0.95 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 114.1, 72.0, 44.2, 29.6, 26.0, 19.9, 18.4, 18.3, –3.64; IR (thin film) 3563, 3458, 2962, 2931, 2859, 1673 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{14}H_{30}O_2SiNa$ $[M + Na]^+$ 281.1913, found 281.1916.



2-21

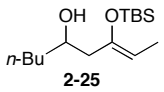
(*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-methylhepta-1,5-dien-3-ol (2-21). Enantioselective reduction: A solution of BH_3•SMe_2 (1.0 M in CH_2Cl_2, 0.23 mL), (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.04 mL) and 3.6 mL toluene was stirred for 10 min at rt, cooled to –40 ºC and stirred for an additional 10 min. A solution of enone **2-110** (91 mg, 0.36 mmol) in 0.8 mL toluene was added dropwise over 5 minutes. The mixture was stirred overnight, warming to 0 ºC. The solution was cooled back down to –40 ºC and an additional portion of BH_3•SMe_2 (1.0 M in CH_2Cl_2, 0.23 mL) was added. The mixture was stirred for 4.5 h slowly warming to –20 ºC. The reaction was quenched with H_2O (1 mL), and the solution was extracted with EtOAc (3 x 2 mL). The combined organic layers was washed with saturated aqueous NaCl (2 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:9 EtOAc:hexanes) afforded enantioenriched alcohol **2-21** (9.0:1.0 *e.r.*) as a clear colorless oil (50 mg, 60%). **Racemic reduction**: $CeCl_3$•$7H_2O$ (160 mg, 0.43 mmol) was added to a vial containing enone **2-110** (100 mg, 0.39 mmol) and MeOH (1.95 mL) at –78 ºC. The mixture was stirred for 10 min then $NaBH_4$ (16 mg, 0.43 mmol) was added and the solution was stirred for an additional 20 min. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with 10 mL saturated aqueous NaCl. The solution was extracted with EtOAc (3 x 15 mL) and the organic layers were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded racemic alcohol **2-21** as a clear colorless oil (94 mg, 94%): R_f = 0.46 (10% EtOAc/hexanes); $[\alpha]^{24}_D$ = 7.5 (*c* 1.97, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.0, 10.7, 6.0 Hz,

1H), 5.26 (d, J = 17.2 Hz, 1H), 5.10 (d, J = 10.5 Hz, 1H), 4.35–4.31 (m, 1H), 2.41 (dd, J = 14.1, 8.8 Hz, 1H), 2.27 (dd, J = 14.1, 4.1 Hz, 1H), 1.64 (app. s, 6H), 0.95 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 140.5, 114.4, 113.6, 71.3, 40.1, 26.0, 19.3, 18.4, 18.3, –3.67, –3.74; IR (thin film) 3417, 2958, 2930, 2859, 1681 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{14}H_{28}O_2SiNa$ [M + Na]$^+$ 279.1756, found 279.1762.



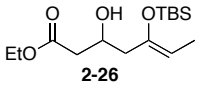
2-22

5-(*tert*-Butyldimethylsilyloxy)-6-methyl-1-phenylhept-5-en-1-yn-3-ol (2-22). Ketone **2-111** (207 mg, 0.63 mmol) was converted to alcohol **2-22** following the general procedure for alcohol **2-15** formation. The mixture was stirred for 1.5 h at –20 ºC and extracted with CH_2Cl_2 instead of EtOAc. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded alcohol **2-22** as a clear light yellow oil (182 mg, 87%): R_f = 0.55 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.30–7.29 (m, 3H), 4.82 (dd, J = 7.7, 5.2 Hz, 1H), 2.73 (dd, J = 14.1, 7.7 Hz, 1H), 2.62 (dd, J = 14.0, 5.1 Hz, 1H), 2.55 (br. s, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 0.97 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 131.8, 128.34, 128.30, 122.9, 114.5, 89.9, 84.6, 61.6, 40.5, 26.0, 19.4, 18.4, 18.3, –3.7, –3.8; IR (thin film) 3390, 2956, 2929, 2858, 1682 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{20}H_{30}O_2SiNa$ [M + Na]$^+$ 353.1913, found 353.1920.



2-25

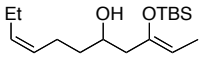
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)non-2-en-5-ol (2-25). Ketone **2-112** (120 mg, 0.44 mmol) was converted to alcohol **2-25** following the general procedure for alcohol **2-24** formation. The mixture was stirred for 1 h at –20 °C. The reaction was quenched with H_2O instead of saturated aqueous NH_4Cl and dried with anhydrous Na_2SO_4 instead of $MgSO_4$. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-25** as a clear colorless oil (109 mg, 91%): R_f = 0.44 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (q, *J* = 6.7 Hz, 1H), 3.80–3.73 (m, 1H), 2.19–2.18 (m, 1H), 2.03 (d, *J* = 2.5 Hz, 1H), 2.00 (dd, *J* = 13.8, 8.8 Hz, 1H), 1.54 (dd, *J* = 6.7, 0.5 Hz, 3H), 1.43–1.32 (m, 6H), 0.96 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 105.6, 69.2, 45.0, 36.6, 28.0, 25.9, 22.9, 18.4, 14.2, 11.1, –3.8; IR (thin film) 3340, 2957, 2931, 2860, 1678 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{32}O_2SiNa$ $[M + Na]^+$ 295.2069, found 295.2075.



2-26

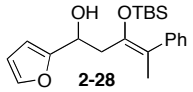
(*Z*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-3-hydroxyhept-5-enoate (2-26). Ketone **2-113** (50 mg, 0.17 mmol) was converted to alcohol **2-26** following the general procedure for alcohol **2-24** formation. EtOH was used as the solvent instead of MeOH, in case transesterification occurred. The mixture was stirred for 2 h at –40 °C. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-26** as a clear yellow oil (47 mg, 96%): R_f = 0.32 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (q, *J* = 6.9 Hz, 1H), 4.24–4.18 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.88 (d, *J* = 2.9 Hz, 1H), 2.53 (dd, *J* = 16.2, 3.9 Hz,

1H), 2.42 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.25 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.16 (dd, *J* =14.0, 6.0 Hz, 1H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 147.5, 105.9, 66.1, 60.7, 44.0, 40.9, 25.9, 18.4, 14.3, 11.1, –3.8, –3.9; IR (thin film) 3461, 2956, 2931, 2859, 1736, 1677 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{30}O_4SiNa$ $[M + Na]^+$ 325.1811, found 325.1803.



2-27

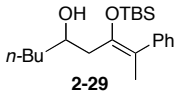
(2*Z*,8*Z*)-3-(*tert*-Butyldimethylsilyloxy)undeca-2,8-dien-5-ol (2-27). Ketone **2-114** (50 mg, 0.17 mmol) was converted to alcohol **2-27** following the general procedure for alcohol **2-24** formation. The mixture was stirred for 1 h at –20 ºC. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded alcohol **2-27** (43 mg, 85%): R_f = 0.48 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41–5.31 (m, 2H), 4.61 (q, *J* = 6.5 Hz, 1H), 3.86–3.76 (m, 1H), 2.20–2.01 (m, 3H), 2.09–2.01 (m, 4H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.53–1.43 (m, 2H), 0.97–0.92 (m, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 132.4, 128.7, 105.6, 68.8, 45.0, 36.9, 26.0, 23.6, 20.7, 18.4, 14.5, 11.1, –3.8; IR (thin film) 3375, 3006, 2961, 2932, 2859, 1676 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{17}H_{34}O_2SiNa$ $[M + Na]^+$ 321.2226, found 321.2223.



2-28

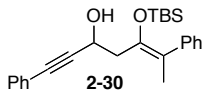
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-1-(furan-2-yl)-4-phenylpent-3-en-1-ol (2-28). Ketone **2-115** (58 mg, 0.16 mmol) was converted to alcohol **2-28** following the general procedure for alcohol **2-24** formation. The mixture was stirred for 3 h at –20 ºC. Purification by column

chromatography (15:85 EtOAc:hexanes) of the crude residue afforded alcohol **2-28** as a clear colorless oil (58 mg, quant.): R_f = 0.40 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.45 (m, 1H), 7.34–7.28 (m, 4H), 7.26–7.20 (m, 1H), 6.42–6.38 (m, 2H), 5.15 (dd, J = 7.4, 5.7 Hz, 1H), 2.92 (dd, J = 13.8, 8.0 Hz, 1H), 2.82 (dd, J = 13.9, 5.3 Hz, 1H), 2.70 (br. s, 1H), 1.97 (s, 3H), 0.82 (s, 9H), –0.17 (s, 3H), –0.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 142.5, 142.1, 142.0, 129.4, 127.9, 126.1, 118.9, 110.4, 106.2, 66.9, 39.4, 25.8, 19.4, 18.1, –4.4, –4.5; IR (thin film) 3396, 2954, 2928, 2857, 1659, 1600 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{21}H_{30}O_3SiNa$ $[M + Na]^+$ 381.1862, found 381.1870.



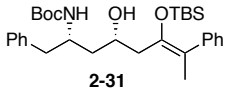
2-29

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-phenylnon-2-en-5-ol (2-29). Ketone **2-116** (325 mg, 0.94 mmol) was converted to alcohol **2-29** following the general procedure for alcohol **2-24** formation. The mixture was stirred for 1 h at –20 ºC. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-29** as a clear yellow oil (277 mg, 84%): R_f = 0.56 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 4H), 7.15 (app. sextet, J = 4.3 Hz, 1H), 4.00–3.94 (m, 1H), 2.45–2.36 (m, 2H), 1.98 (s, 3H), 1.58–1.52 (m, 2H), 1.50–1.45 (m, 1H), 1.43–1.33 (m, 3H), 0.93 (t, J = 7.0 Hz, 3H), 0.74 (s, 9H), –0.25 (s, 3H), –0.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 142.2, 129.4, 127.9, 126.1, 118.0, 70.8, 40.7, 36.8, 28.1, 25.8, 22.9, 19.6, 18.1, 14.2, –4.3, –4.4; IR (thin film) 3388, 2930, 2856, 2858, 1651 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{21}H_{36}O_2SiNa$ $[M + Na]^+$ 371.2382, found 371.2379.



2-30

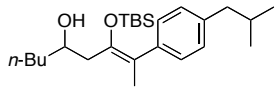
(*Z*)-5-(*tert*-Butyldimethylsilyloxy)-1,6-diphenylhept-5-en-1-yn-3-ol (2-30). Ketone **2-117** (130 mg, 0.33 mmol) was converted to alcohol **2-30** following the general procedure for alcohol **2-24** formation. The mixture was stirred for 2 h at –20 ºC. Purification by column chromatography (15:85 EtOAc:hexanes) of the crude residue afforded alcohol **2-30** as a clear yellow oil (82 mg, 63%): R_f = 0.44 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.31–7.24 (m, 7H), 7.18–7.14 (m, 1H), 4.98–4.94 (m, 1H), 2.83 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.76 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.62 (br. s, 1H), 2.06 (s, 3H), 0.75 (s, 9H), –0.22 (s, 3H), –0.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 142.1, 131.8, 129.4, 128.45, 128.38, 128.0, 126.2, 122.8, 119.3, 89.6, 85.0, 62.1, 41.1, 25.8, 19.9, 18.1, –4.4, –4.5; IR (thin film) 3350, 2954, 2928, 2894, 2857, 1655 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{25}H_{32}O_2SiNa$ $[M + Na]^+$ 415.2069, found 415.2067.



2-31

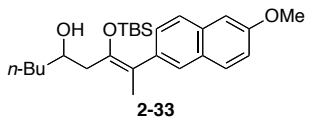
***tert*-Butyl (2*S*,4*S*,*Z*)-6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-1,7-diphenyloct-6-en-2-ylcarbamate (2-31).** A solution of L-Selectride (0.25 mL, 0.25 mmol, 1.0 M in THF) was added dropwise to a solution of ketone **2-118** (110 mg, 0.21 mmol) in 2.1 mL THF at –78 ºC. The mixture was stirred for 4 h and at –78 ºC and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 x 10 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded alcohol **2-31** as a clear colorless oil (63 mg, 56%): R_f = 0.40 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = 3.2 (*c* 3.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.30–7.14 (m, 10H), 4.79–4.74 (m, 1H), 4.11–4.04 (m, 1H), 4.03–3.95 (m, 1H), 2.96–2.89 (m, 1H), 2.85–2.79 (m, 2H), 2.44–2.36 (m, 2H), 1.92 (s, 3H), 1.84–1.77 (m, 1H), 1.62–1.55 (m, 1H), 1.42 (s, 9H), 0.72 (s, 9H), 0.30 (d, J = 8.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 143.5, 142.1, 138.1, 129.8, 129.4, 128.5, 127.9, 126.5, 126.1, 118.2, 79.4, 69.4, 50.4, 41.7, 40.7, 40.6, 28.5, 25.8, 19.6, 18.0, –4.4; IR (thin film) 3408, 3058, 3025, 2955, 2929, 2857, 1693 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{31}H_{47}NO_4SiNa$ [M + Na]$^+$ 548.3172, found 548.3184.



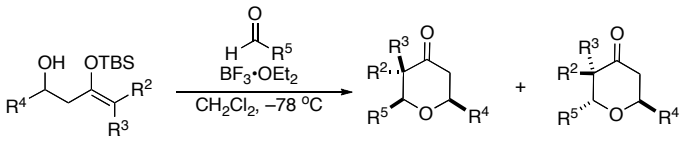
2-32

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(4-isobutylphenyl)non-2-en-5-ol (2-32). Ketone **2-119** (126 mg, 0.31 mmol) was converted to alcohol **2-32** following the general procedure for alcohol **2-24** formation. The mixture was stirred for 4 h at –20 ºC and extracted with CH_2Cl_2 instead of EtOAc. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-32** as a clear light yellow oil (122 mg, 97%): R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 4.00–3.95 (m, 1H), 2.44 (d, J = 7.2 Hz, 2H), 2.42–2.36 (m, 2H), 2.32 (br. s, 1H), 1.98 (s, 3H), 1.84 (app. septet, J = 6.7 Hz, 1H), 1.60–1.36 (m, 6H), 0.94 (t, J = 7.1 Hz, 3H), 0.90 (d, J = 6.8 Hz, 6H), 0.75 (s, 9H), –0.24 (s, 3H), –0.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 139.5, 139.4, 129.1, 128.7, 118.0, 70.8, 45.3, 40.8, 36.8, 30.4, 28.1, 25.9, 22.9, 22.4, 19.6, 18.1, 14.2, –4.3, –4.4; IR (thin film) 3400, 2955, 2929, 2859, 1652 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{25}H_{44}O_2SiNa$ [M + Na]$^+$427.3008, found 427.3010.

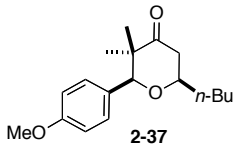


2-33

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(6-methoxynaphthalen-2-yl)non-2-en-5-ol (2-33). Ketone **2-120** (51 mg, 0.12 mmol) was converted to alcohol **2-33** following the general procedure for alcohol **2-24** formation. The mixture was stirred for 4 h at –20 ºC and extracted with CH_2Cl_2 instead of EtOAc. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded alcohol **2-33** as a clear light yellow oil (40 mg, 79%): R_f = 0.30 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.64 (m, 3H), 7.41 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.12–7.10 (m, 2H), 4.05–3.99 (m, 1H), 3.92 (s, 3H), 2.50–2.42 (m, 2H), 2.32 (br. s, 1H), 2.07 (s, 3H), 1.63–1.36 (m, 6H), 0.95 (t, *J* = 7.1 Hz, 3H), 0.72 (s, 9H), –0.29 (s, 3H), –0.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 144.4, 137.4, 133.1, 129.4, 128.9, 128.6, 127.7, 126.1, 118.6, 117.8, 105.6, 70.9, 55.4, 40.9, 36.9, 28.1, 25.9, 22.9, 19.6, 18.1, 14.2, –4.2, –4.3; IR (thin film) 3444, 2956, 2929, 2858, 1604 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{26}H_{40}O_3SiNa$ [M + Na]$^+$ 451.2644, found 451.2645.

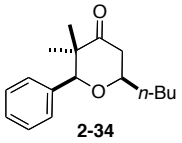


General Procedure for THPO Formation. BF_3•OEt_2 (1.5 equiv) was added dropwise to a solution of aldehyde (1.5 equiv) and hydroxy silyl enol ether (1.0 equiv) in CH_2Cl_2 (1.0 M relative to the silyl enol ether) at –78 ºC. The mixture was stirred for 4 h, and the reaction was quenched with saturated aqueous $NaHCO_3$. The solution was extracted with CH_2Cl_2 (3 x) and the organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography of the crude residue afforded desired THPO.



2-37

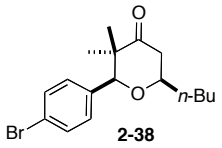
6-Butyl-2-(4-methoxyphenyl)-3,3-dimethyldihydro-2H-pyran-4(3H)-one (2-37). Alcohol **2-17** (46 mg, 0.16 mmol) and 4-anisaldehyde (32 μL, 0.26 mmol) were converted to THPO **2-37** following the general procedure for THPO formation. The solution was extracted with EtOAc instead of CH_2Cl_2. Purification by column chromatography (1:19 EtOAc:hexanes) of the crude residue afforded THPO **2-37** as a clear colorless oil (32 mg, 69%): R_f = 0.37 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.27 (s, 1H), 3.81 (s, 3H), 3.74–3.68 (m, 1H), 2.67 (dd, J = 14.2, 11.8 Hz, 1H), 2.34 (dd, J = 14.2, 2.7 Hz, 1H), 1.77–1.71 (m, 1H), 1.64–1.59 (m, 1H), 1.44–1.31 (m, 4H), 1.01 (s, 3H), 0.91 (s, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.5, 159.2, 129.7, 129.1, 113.1, 85.8, 77.8, 55.4, 50.6, 44.5, 36.3, 27.3, 22.8, 19.9, 19.5, 14.1; IR (thin film) 2958, 2933, 2860, 1712, 1613 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{18}H_{26}O_3Na$ $[M + Na]^+$ 291.1960, found 291.1958.



2-34

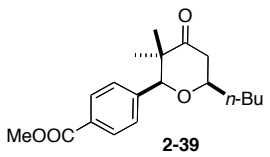
6-Butyl-3,3-dimethyl-2-phenyldihydro-2H-pyran-4(3H)-one (2-34). A sample of alcohol **2-17** (46 mg, 0.16 mmol) and benzaldehyde (28 mg, 0.26 mmol) was converted to **2-34** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-34** as a clear colorless oil (20 mg, 47%): R_f = 0.63 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 4.32 (s, 1H),

3.76–3.70 (m, 1H), 2.69 (dd, *J* = 14.2, 11.8 Hz, 1H), 2.36 (dd, *J* = 14.2, 2.7 Hz, 1H), 1.77–1.72 (m, 1H), 1.66–1.59 (m, 1H), 1.46–1.30 (m, 4H), 1.01 (s, 3H), 0.94 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.3, 137.5, 128.1, 127.8, 127.7, 86.4, 77.8, 50.4, 44.5, 36.3, 27.3, 22.8, 19.9, 19.5, 14.1; IR (neat) 2932, 1712 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{17}H_{25}O_2$ $[M + H]^+$ 261.1855, found 261.1855.



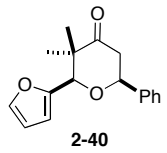
2-38

2-(4-Bromophenyl)-6-butyl-3,3-dimethyldihydro-2H-pyran-4(3H)-one (2-38). A sample of alcohol **2-17** (46 mg, 0.16 mmol) and 4-bromobenzaldehyde (48 mg, 0.26 mmol) was converted to **2-38** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-38** as a clear colorless oil (23 mg, 43%): R_f = 0.58 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 4.28 (s, 1H), 3.75–3.69 (m, 1H), 2.67 (dd, *J* = 14.2, 11.9 Hz, 1H), 2.36 (dd, *J* = 14.3, 2.7 Hz, 1H), 1.76–1.72 (m, 1H), 1.63–1.58 (m, 1H), 1.44–1.31 (m, 4H), 0.98 (s, 3H), 0.92 (s, 3H), 0.89 (t, *J* = 7.05 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.9, 136.4, 130.9, 129.7, 121.8, 85.5, 77.9, 50.2, 44.4, 36.3, 27.3, 22.7, 19.8, 19.5, 14.2; IR (neat) 2958, 2932, 2860, 1713 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{17}H_{24}BrO_2$ $[M + H]^+$ 339.0960, 341.0941, found 339.0954, 341.0954.



2-39

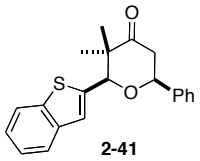
Methyl 4-6-butyl-3,3-dimethyl-4-oxotetrahydro-2*H*-pyran-2-yl)benzoate (2-39). Alcohol **2-17** (46 mg, 0.16 mmol) and methyl-4-formylbenzoate (43 mg, 0.26 mmol) were converted to **2-39** following the general procedure for THPO formation. Purification by column chromatography (1:19 EtOAc:hexanes) of the crude residue afforded THPO **2-39** as a clear colorless oil (18 mg, 35%): R_f = 0.27 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 4.38 (s, 1H), 3.92 (s, 3H), 3.77–3.72 (m, 1H), 2.68 (dd, *J* = 14.2, 11.9 Hz, 1H), 2.38 (dd, *J* = 14.4, 2.6 Hz, 1H), 1.79–1.73 (m, 1H), 1.66–1.59 (m, 1H), 1.46–1.31 (m, 4H), 0.98 (s, 3H), 0.94 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.6, 167.1, 142.5, 129.7, 129.0, 128.0, 85.7, 78.0, 52.3, 50.2, 44.4, 36.3, 27.3, 22.8, 19.9, 19.5, 14.1; IR (neat) 2956, 2360, 1722, 1715 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{19}H_{30}NO_4$ $[M + NH_4]^+$ 336.2175, found 336.2168.



2-40

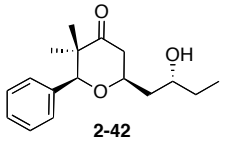
2-(Furan-2-yl)-3,3-dimethyl-6-phenyldihydro-2H-pyran-4(3H)-one (2-40). Alcohol **2-18** (50 mg, 0.16 mmol) and furan-2-carbaldehyde (24 mg, 0.25 mmol) were converted to **2-40** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-40** as a clear colorless oil (28 mg, 63%): R_f = 0.38 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.30 (m, 6H), 6.41–6.38 (m, 2H), 4.78 (dd, *J* = 12.0, 2.7 Hz, 1H), 4.60 (s, 1H), 2.99 (dd, *J* = 14.5, 12.1 Hz, 1H), 2.62

(dd, J = 14.5, 2.9 Hz, 1H), 1.30 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 151.0, 142.2, 140.8, 128.8, 128.3, 125.8, 110.3, 109.0, 81.0, 79.6, 50.2, 46.3, 20.6, 19.0; IR (neat) 3118, 3033, 2974, 2934, 2873, 1714 cm^{-1}; HRMS (ES/MeOH) m / z calc for $C_{17}H_{22}O_3N$ $[M + NH_4]^+$ 288.1600, found 288.1600.



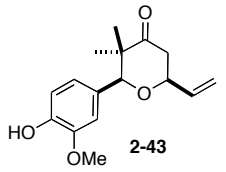
2-41

2-(Benzo[*b*]thiophen-2-yl)-3,3-dimethyl-6-phenyldihydro-2*H*-pyran-4(3*H*)-one (2-41). Alcohol **2-18** (50 mg, 0.16 mmol) and 1-(1-benzothien-3-yl)ethanone (41 mg, 0.25 mmol) were converted to **2-41** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-41** as a clear colorless oil (21 mg, 38%) and recovered alcohol **2-18** (34 mg): R_f = 0.36 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2H), 7.57 (s, 1H), 7.48–7.46 (m, 2H), 7.41–7.38 (m, 3H), 7.36–7.31 (m, 2H), 5.06 (s, 1H), 4.87 (dd, J = 12.0, 2.8 Hz, 1H), 3.08 (dd, J = 14.5, 12.1 Hz, 1H), 2.71 (dd, J = 14.4, 2.9 Hz, 1H), 1.31 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1, 141.0, 140.1, 138.3, 132.5, 128.8, 128.3, 125.7, 124.4, 124.2, 122.93, 122.88, 81.9, 79.8, 51.3, 46.3, 20.7, 19.9; IR (thin film) 2972, 1710 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{21}H_{24}O_2SN$ $[M + NH_4]^+$ 354.1528, found 354.1535.



2-42

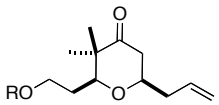
(2*S*,6*R*)-6-((*R*)-2-hydroxybutyl)-3,3-dimethyl-2-phenyldihydro-2H-pyran-4(3H)-one (2-42). Alcohol **2-19** (93 mg, 0.31 mmol) and benzaldehyde (53 mg, 0.50 mmol) were converted to **2-42** following the general procedure for THPO formation. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded THPO **2-42** as a yellow oil (55 mg, 64%): R_f = 0.28 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = 38.6 (*c* 0.86, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 5H), 4.42 (s, 1H), 4.06–4.01 (m, 1H), 3.79–3.75 (m, 1H), 3.42 (s, 1H), 2.78 (dd, *J* = 14.4, 12.0 Hz, 1H), 2.40 (dd, *J* = 14.4, 2.6 Hz, 1H), 1.89 (app. dt, *J* = 14.6, 9.8 Hz, 1H), 1.73 (dt, *J* = 14.6, 2.0 Hz, 1H), 1.57–1.44 (m, 2H), 1.04 (s, 3H), 0.96 (s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.7, 136.6, 128.2, 128.0, 127.7, 86.4, 79.0, 72.9, 50.5, 44.8, 42.9, 30.4, 19.8, 19.4, 9.9; IR (neat) 3491, 2970, 2935, 2877, 1712 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1630.



2-43

2-(4-Hydroxy-3-methoxyphenyl)-3,3-dimethyl-6-vinyldihydro-2*H*-pyran-4(3*H*)-one (2-43). Alcohol **2-21** (43 mg, 0.16 mmol) and vanillin (38 mg, 0.25 mmol) were converted to **2-43** following the general procedure for THPO formation. Purification by column chromatography (gradient: 1:9 to 1:1 EtOAc:hexanes) of the crude residue afforded THPO **2-43** as a clear colorless oil (13 mg, 30%): R_f = 0.78 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 5.0, 3.2 Hz, 2H), 6.81 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.00 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H),

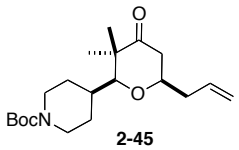
5.59 (s, 1H), 5.35 (app. dt, J = 9.3, 5.8 Hz, 1H), 5.22 (app. dt, J = 5.9, 3.5 Hz, 1H), 4.34 (s, 1H), 4.28–4.24 (m, 1H), 3.91 (s, 3H), 2.79 (dd, J = 14.3, 12.0 Hz, 1H), 2.44 (dd, J = 14.3, 2.9 Hz, 1H), 1.06 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 146.0, 145.5, 137.4, 129.1, 121.3, 116.2, 113.7, 110.7, 86.1, 78.1, 56.2, 50.7, 44.2, 20.0, 19.6; IR (thin film) 3418, 2970, 2934, 1712, 1604 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{16}H_{21}O_4$ [M + H]$^+$ 277.1440, found 277.1450.



2-44

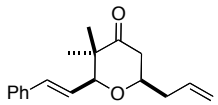
THPO 2-44. Alcohol **2-16** (49 mg, 0.18 mmol) and 3-(*tert*-butyldimethylsilyloxy)propanal (53 mg, 0.28 mmol) were converted to **2-44** following the general procedure for THPO formation. TMSOTf was used as the Lewis acid instead of BF_3•OEt_2. Purification by column chromatography (gradient: 1:9 to 1:0 EtOAc:hexanes) of the crude residue afforded THPO **2-44** as a clear colorless oil (Overall: 35 mg, 76%): **For R=H**: Isolated 18.2 mg, 48%, R_f = 0.51 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85–5.76 (m, 1H), 5.16–5.12 (m, 2H), 3.82–3.78 (m, 2H), 3.75–3.70 (m, 1H), 3.48 (dd, J = 10.7, 2.1 Hz, 1H), 2.65 (t, J = 5.5 Hz, 1H), 2.56 (dd, J = 14.4, 11.9 Hz, 1H), 2.40–2.33 (m, 2H), 2.29 (dd, J = 14.4, 2.7 Hz, 1H), 1.85–1.93 (m, 1H), 1.67–1.62 (m, 1H), 1.13 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1, 133.5, 118.6, 84.9, 77.1, 62.0, 49.2, 44.1, 40.8, 31.1, 19.5, 18.9; IR (thin film) 3416, 3078, 2969, 2934, 2875, 1712, 1642 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{12}H_{21}O_3$ [M + H]$^+$ 213.1491, found 213.1490. **For R=TBS**: Isolated 16.5 mg, 28%, R_f = 0.46 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (tdd, J = 17.1, 10.2, 7.0 Hz, 1H), 5.18–5.14 (m, 2H), 3.84–3.78 (m, 2H), 3.69–3.63 (m, 1H), 3.46 (dd, J = 6.8, 5.3 Hz, 1H), 2.58 (dd, J = 14.4, 11.8 Hz, 1H),

2.48–2.43 (m, 1H), 2.38–2.32 (m, 1H), 2.32 (dd, *J* =14.3, 2.7 Hz, 1H), 1.76–1.72 (m, 2H), 1.15 (s, 3H), 1.05 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.3, 133.7, 117.8, 80.2, 76.8, 59.9, 49.0, 44.2, 40.7, 32.7, 26.1, 19.4, 18.9, 18.4, –5.2, –5.3; IR (thin film) 2958, 2930, 2857, 1714, 1643 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{34}O_3SiNa$ $[M + Na]^+$ 349.2175, found 349.2173.



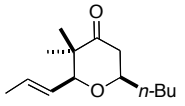
2-45

***tert*-Butyl 4-(-6-allyl-3,3-dimethyl-4-oxotetrahydro-2H-pyran-2-yl)piperidine-1-carboxylate (2-45).** Alcohol **2-16** (49 mg, 0.18 mmol) and *tert*-butyl-4-formylpiperidine1-carboxylate (60 mg, 0.28 mmol) were converted to **2-45** following the general procedure for THPO formation using TMSOTf instead of $BF_3{\cdot}OEt_2$. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded THPO **2-45** as a clear colorless oil (28 mg, 42%): R_f = 0.62 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88–5.80 (m, 1H), 5.11–5.08 (m, 2H), 4.16–4.01 (br. s, 2H), 3.58–3.53 (m, 1H), 2.96 (d, *J* = 2.9 Hz, 1H), 2.76–2.63 (m, 2H), 2.50 (dd, *J* = 14.3, 11.7 Hz, 1H), 2.39–2.29 (m, 2H), 2.23 (dd, *J* =14.3, 2.8 Hz, 1H), 1.80–1.71 (m, 2H), 1.60–1.49 (m, 3H), 1.45 (s, 9H), 1.15 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.8, 155.0, 133.7, 117.9, 86.9, 79.4, 77.0, 50.5, 44.0, 40.6, 37.2, 32.3, 28.6, 27.9, 20.5, 19.4; IR (neat) 2973, 2933, 2852, 1711, 1693 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{20}H_{33}NO_4Na$ $[M + Na]^+$ 374.2307, found 374.2305.



2-46

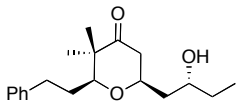
6-Allyl-3,3-dimethyl-2-styryldihydro-2*H*-pyran-4(3*H*)-one (2-46). Alcohol **2-16** (49 mg, 0.18 mmol) and cinnamaldehyde (37 mg, 0.28 mmol) were converted to **2-46** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-46** as a clear colorless oil (44 mg, 91%): R_f = 0.50 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32 (app. t, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.29 (dd, *J* = 16.0, 6.6 Hz, 1H), 5.94 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.23–5.19 (m, 2H), 4.00 (d, *J* = 6.6 Hz, 1H), 3.83 (dtd, *J* = 11.8, 9.2, 4.3 Hz, 1H), 2.70 (dd, *J* = 14.4, 11.9 Hz, 1H), 2.58–2.43 (m, 2H), 2.38 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.23 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 136.7, 133.6, 133.4, 128.7, 128.0, 126.7, 124.3, 118.3, 85.0, 76.8, 49.7, 43.9, 40.7, 19.9, 19.2; IR (thin film) 3080, 3026, 2976, 2933, 2850, 1713 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{23}O_2$ $[M + H]^+$ 271.1698, found 271.1690.



2-47

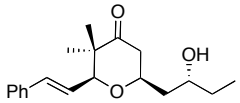
6-Butyl-3,3-dimethyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-47). Alcohol **2-17** (1.92 g, 6.70 mmol) and crotonaldehyde (0.70 g, 10 mmol) were converted to **2-47** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-47** as a clear light yellow oil (1.09 g, 73%): R_f = 0.51 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78–5.72 (m, 1H), 5.53 (dq, *J* = 15.3, 2.9 Hz, 1H), 3.67 (d, *J* = 7.2 Hz, 1H), 3.61–3.58 (m, 1H), 2.53 (dd, *J* = 14.2, 11.8

Hz, 1H), 2.26 (dd, *J* = 14.2, 2.6 Hz, 1H), 1.75–1.74 (m, 3H), 1.73–1.66 (m, 1H), 1.58–1.50 (m, 1H), 1.44–1.37 (m, 1H), 1.36–1.28 (m, 3H), 1.11 (s, 3H), 0.94 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4, 130.7, 126.1, 85.3, 77.5, 49.5, 44.6, 36.3, 27.4, 22.8, 19.8, 19.2, 18.2, 14.1; IR (thin film) 2961, 2933, 2860, 1713 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{14}H_{25}O_2$ $[M + H]^+$ 225.1855, found 225.1857.



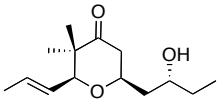
2-48

(2*S*,6*R*)-6-((*R*)-2-hydroxybutyl)-3,3-dimethyl-2-phenethyldihydro-2*H*-pyran-4(3*H*)-one (2-48). Diol **2-19** (50 mg, 0.16 mmol) and dihydrocinnamaldehyde (33 mg, 0.24 mmol) were converted to **2-48** following the general procedure for THPO formation. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded THPO **2-48** as a yellow oil (28 mg, 56%): R_f = 0.50 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ = –96.5 (*c* 0.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.21–7.18 (m, 3H), 3.86–3.80 (m, 2H), 3.35 (s, 1H), 3.27 (d, *J* = 9.9 Hz, 1H), 2.92–2.87 (m, 1H), 2.65–2.56 (m, 2H), 2.28 (dd, *J* = 14.3, 2.4 Hz, 1H), 1.93–1.85 (m, 1H), 1.85–1.73 (m, 2H), 1.69–1.66 (m, 2H), 1.59–1.51 (m, 1H), 1.11 (s, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9, 141.4, 128.7, 128.6, 126.2, 83.7, 78.4, 72.8, 49.5, 45.0, 42.7, 33.0, 31.1, 30.3, 19.4, 18.9, 9.8; IR (neat) 3491, 2966, 2931, 2873, 2858, 1712 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{19}H_{28}O_3Na$ $[M + Na]^+$ 327.1936, found 327.1940.



2-49

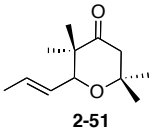
(2*S*,6*R*)-6-((*R*)-2-hydroxybutyl)-3,3-dimethyl-2-styryldihydro-2*H*-pyran-4(3*H*)-one (2-49). Diol **2-19** (50 mg, 0.16 mmol) and cinnamaldehyde (33 mg, 0.25 mmol) were converted to **2-49** following the general procedure for THPO formation. Purification by column chromatography (3:7 EtOAc:hexanes) of the crude residue afforded THPO **2-49** as a clear colorless oil (48 mg, 97%): R_f = 0.52 (30% EtOAc/hexanes); $[\alpha]^{24}_{D}$ = –20.0 (*c* 1.39, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.38 (m, 2H), 7.34–7.33 (m, 2H), 7.31–7.25 (m, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.20 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.01 (d, *J* = 6.9 Hz, 1H), 4.01–3.95 (m, 1H), 3.82–3.78 (m, 1H), 3.37 (br. s, 1H), 2.68 (dd, *J* = 14.3, 12.0 Hz, 1H), 2.35 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.87–1.81 (m, 1H), 1.69 (dt, *J* = 8.5, 4.8 Hz, 1H), 1.55–1.46 (m, 2H), 1.18 (s, 3H), 1.05 (s, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6, 136.3, 134.1, 128.8, 128.2, 126.7, 123.7, 85.3, 78.5, 72.8, 49.9, 44.9, 42.7, 30.4, 19.9, 19.2, 9.9; IR (neat) 3456, 3026, 2967, 2933, 2874, 1711 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{19}H_{26}O_3Na$ $[M + Na]^+$ 325.1780, found 325.1782.



2-50

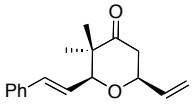
(2*S*,6*R*)-6-((*R*)-2-Hydroxybutyl)-3,3-dimethyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-50). Diol **2-19** (50 mg, 0.16 mmol) and crotonaldehyde (18 mg, 0.26 mmol) were converted to **2-50** following the general procedure for THPO formation. Purification by column chromatography (3:7 EtOAc:hexanes) of the crude residue afforded THPO **2-50** as a clear colorless oil (26 mg, 65%): R_f = 0.42 (30% EtOAc/hexanes); $[\alpha]^{24}_{D}$ = –24.5 (*c* 1.30, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76–5.67 (m, 1H), 5.49 (ddq, *J* = 15.4, 7.1, 1.8 Hz, 1H), 3.89 (ddt,

J = 12.1, 9.4, 4.7 Hz, 1H), 3.79–3.72 (m, 2H), 3.52 (br. s, 1H), 2.61 (dd, *J* = 14.4, 11.9 Hz, 1H), 2.28 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.73–1.71 (m, 3H), 1.66–1.62 (m, 2H), 1.54–1.43 (m, 2H), 1.11 (s, 3H), 0.95 (s, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.0, 131.1, 125.4, 85.4, 78.5, 72.9, 49.6, 44.9, 42.6, 30.4, 19.7, 19.1, 18.1, 9.9; IR (thin film) 3468, 2967, 2936, 2875, 1712 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{14}H_{25}O_3$ $[M + H]^+$ 241.1804, found 241.1812.



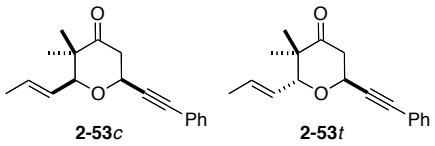
2-51

(*E*)-2,2,5,5-Tetramethyl-6-(prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-51). A sample alcohol **2-20** (80 mg, 0.31 mmol) and crotonaldehyde (34 mg, 0.48 mmol) was converted to **2-51** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-51** as a clear colorless oil (50 mg, 80%): R_f = 0.49 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73–5.68 (m, 1H), 5.53–5.49 (ddq, *J* = 15.3, 7.5, 1.6 Hz, 1H), 3.92 (d, *J* = 7.6 Hz, 1H), 2.69 (d, *J* = 13.7 Hz, 1H), 2.18 (d, *J* = 13.7 Hz, 1H), 1.72 (d, *J* = 6.45 Hz, 3H), 1.36 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 0.92 (s, 3H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.8, 130.8, 126.5, 79.6, 75.0, 49.7, 48.8, 31.2, 24.2, 19.7, 19.3, 18.1; IR (neat) 2972, 2934, 2875, 1713 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calc for $C_{12}H_{24}NO_2$ $[M + NH_4]^+$ 214.1807, found 214.1803.



2-52

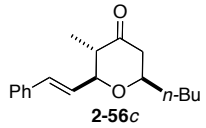
(2*S*,6*S*)-3,3-Dimethyl-2-styryl-6-vinyldihydro-2*H*-pyran-4(3*H*)-one (2-52). Alcohol **2-21** (47 mg, 0.18 mmol) and cinnamaldehyde (36 mg, 0.27 mmol) were converted to **2-52** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-52** as a clear colorless oil (29 mg, 62%): R_f = 0.43 (10% EtOAc/hexanes); $[\alpha]^{24}_{D}$ = –24.7 (*c* 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (app. t, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 16.0, 6.7 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.6, 5.6 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.6 Hz, 1H), 4.24–4.20 (m, 1H), 4.00 (dd, *J* = 6.7, 0.6 Hz, 1H), 2.72 (dd, *J* = 14.3, 12.0 Hz, 1H), 2.40 (dd, *J* = 14.4, 2.8 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.0, 137.3, 136.6, 133.8, 128.7, 128.0, 126.7, 124.1, 116.5, 85.0, 76.9, 49.9, 44.2, 19.9, 19.2; IR (thin film) 3026, 2972, 2933, 2843, 1713 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{17}H_{24}O_2N$ $[M + NH_4]^+$ 274.1807, found 274.1821.



2-53*c* **2-53*t***

3,3-Dimethyl-6-(phenylethynyl)-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-53). Alcohol **2-22** (90 mg, 0.27 mmol) and crotonaldehyde (29 mg, 0.41 mmol) were converted to **2-53** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-53** as a clear colorless oil (51 mg, 71%) in a 4.1:1.0 *cis:trans* ratio. A small amount of THPO **2-53*c*** and

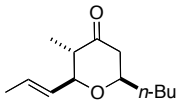
THPO **2-53*t*** was separated for characterization but most was recovered as a mixture of the two diastereomers: **THPO 2-53*c***: R_f = 0.57 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.33–7.26 (m, 3H), 5.84–5.77 (m, 1H), 5.59 (app. ddq, *J* = 15.4, 7.6, 1.6 Hz, 1H), 4.63 (dd, *J* = 12.2, 3.0 Hz, 1H), 3.77 (d, *J* = 7.6 Hz, 1H), 3.06 (dd, *J* = 14.6, 12.2 Hz, 1H), 2.59 (dd, *J* = 14.7, 3.0 Hz, 1H), 1.76 (dd, *J* = 15.7, 8.7 Hz, 3H), 1.20 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 132.0, 131.9, 128.9, 128.4, 125.3, 122.2, 86.3, 86.2, 85.6, 67.8, 49.7, 44.8, 19.7, 19.1, 18.1; IR (thin film) 2971, 2934, 2854, 2232, 1715 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{24}O_2N$ $[M + NH_4]^+$ 286.1807, found 286.1796. **THPO 2-53*t***: R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.40 (m, 2H), 7.33–7.26 (m, 3H), 5.83 (dq, *J* = 15.3, 3.0 Hz, 1H), 5.56 (ddq, *J* = 15.3, 7.4, 1.8 Hz, 1H), 5.29 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.42 (d, *J* = 7.4 Hz, 1H), 3.14 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.52 (dd, *J* = 14.2, 1.8 Hz, 1H), 1.76 (dd, *J* = 6.5, 1.1 Hz, 3H), 1.15 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 132.0, 131.7. 128.9, 128.4, 125.6, 122.1, 88.6, 85.6, 80.7, 65.8, 50.1, 43.7, 19.9, 19.7, 18.2; IR (thin film) 2970, 2932, 2872, 1714 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{24}O_2N$ $[M + NH_4]^+$ 286.1807, found 286.1793.



2-56*c*

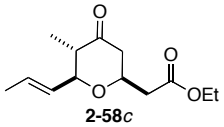
6-Butyl-3-methyl-2-styryldihydro-2*H*-pyran-4(3*H*)-one (2-56*c*). Alcohol **2-25** (40 mg, 0.15 mmol) and cinnamaldehyde (29 mg, 0.22 mmol) were converted to **2-56*c*** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-56** as a clear colorless oil in a 8.3:1.0 *cis:trans* ratio (16 mg, 40%). **THPO 2-56*c***: R_f = 0.43 (10% EtOAc/hexanes); ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.42–7.40 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.28–7.25 (m, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 15.9, 7.4 Hz, 1H), 3.83 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.71–3.66 (m, 1H), 2.49–2.37 (m, 3H), 1.75–1.72 (m 1H), 1.59–1.54 (m, 1H), 1.46–1.32 (m, 4H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.5, 136.4, 133.5, 128.7, 128.2, 127.7, 126.8, 84.4, 76.9, 50.3, 48.2, 36.3, 27.5, 22.7, 14.1, 9.6; IR (thin film) 3026, 2957, 2932, 2860, 1715 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{18}H_{25}O_2$ $[M + H]^+$ 273.1855, found 273.1857.



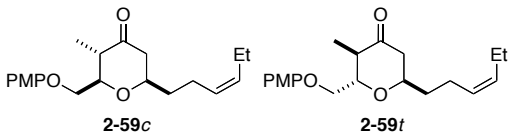
2-57*c*

6-Butyl-3-methyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-57*c*). Alcohol **2-25** (69 mg, 0.25 mmol) and crotonaldehyde (26 mg, 0.37 mmol) were converted to **2-57*c*** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-57** as a clear colorless oil in a 7.0:1.0 *cis:trans* ratio (16 mg, 30%). **THPO 2-57*c***: R_f = 0.51 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dq, *J* = 17.4, 6.5 Hz, 1H), 5.51 (app. dqd, *J* = 15.2, 7.8, 1.8 Hz, 1H), 3.63–3.58 (m, 2H), 2.41 (dd, *J* = 13.6, 2.4 Hz, 1H), 2.37–2.28 (m, 2H), 1.74 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.73–1.66 (m, 1H), 1.56–1.49 (m, 1H), 1.44–1.37 (m, 1H), 1.36–1.28 (m, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 130.6, 130.0, 84.5, 77.6, 50.1, 48.2, 36.3, 27.5, 22.7, 18.0, 14.1, 9.6; IR (thin film) 2959, 2934, 2860, 1717 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{13}H_{26}O_2N$ $[M + NH_4]^+$ 228.1964, found 228.1964.



2-58*c*

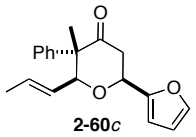
Ethyl 2-(5-methyl-4-oxo-6-((*E*)-prop-1-enyl)tetrahydro-2*H*-pyran-2-yl)acetate (2-58*c*). Alcohol **2-26** (46 mg, 0.15 mmol) and crotonaldehyde (16 mg, 0.23 mmol) were converted to **2-58*c*** following the general procedure for THPO formation. TMSOTf was used as the Lewis acid instead of BF_3•OEt_2. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded THPO **2-58** as a clear colorless oil in a 5.6:1.0 *cis:trans* ratio (18 mg, 49%). **THPO 2-58*c***: R_f = 0.45 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78–5.68 (m, 1H), 5.48 (app. ddq, *J* = 14.8, 7.3, 1.8 Hz, 1H), 4.17–4.06 (m, 3H), 3.66 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.72 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.53–2.48 (m, 2H), 2.42 (dd, *J* = 11.6, 1.1 Hz, 1H), 2.33–2.26 (m, 1H), 1.73 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.5, 170.2, 131.0, 129.6, 84.3, 73.6, 60.9, 49.8, 47.4, 41.4, 17.9, 14.3, 9.6; IR (thin film) 2977, 2935, 2877, 1736, 1717 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{13}H_{20}O_4Na$ [M + Na]$^+$ 263.1259, found 263.1258.



2-59*c* **2-59*t***

6-((*Z*)-Hex-3-enyl)-2-((4-methoxyphenoxy)methyl)-3-methyldihydro-2*H*-pyran-4(3*H*)-one. (2-59). Alcohol **2-27** (46 mg, 0.15 mmol) and 2-(4-methoxyphenoxy)acetaldehyde (38 mg, 0.23 mmol) were converted to **2-59** following the general procedure for THPO formation using TMSOTf instead of BF_3•OEt_2. Purification by column chromatography (1:4 EtOAc:hexanes) of the crude residue afforded THPO **2-59*c*** (28 mg, 55%) and **2-59*t*** (8 mg, 17%) as a clear colorless oil. **THPO 2-59*c***: R_f = 0.42 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83–6.78 (m,

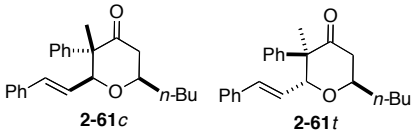
4H), 5.54–5.47 (m, 1H), 5.22 (ddd, *J* = 15.3, 8.7, 1.5 Hz, 1H), 4.02 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.85 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.82–3.77 (m, 1H), 3.76 (s, 3H), 3.42 (ddd, *J* = 10.2, 6.1, 2.0 Hz, 1H), 2.75 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.54–2.40 (m, 3H), 2.19–2.12 (m, 1H), 1.82 (dq, *J* = 13.2, 3.5 Hz, 1H), 1.69 (dq, *J* = 12.7, 4.3 Hz, 1H), 1.62 (dd, *J* = 6.4, 1.5 Hz, 3H), 1.46 (m, 1H), 1.37–1.29 (m, 1H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.3, 153.9, 153.5, 131.6, 127.2, 116.0, 114.6, 80.2, 74.4, 70.8, 55.8, 49.0, 41.0, 37.2, 31.2, 30.8, 18.2, 7.7; IR (thin film) 2935, 2918, 2876, 2854, 1714, 1508 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{20}H_{28}O_4Na$ $[M + Na]^+$ 355.1885, found 355.1878. **THPO 2-59*t***: R_f = 0.53 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91–6.89 (m, 2H), 6.84–82 (m, 2H), 5.42–5.37 (m, 1H), 5.31–5.26 (m, 1H), 4.22 (ddd, *J* = 10.6, 2.0 Hz, 1H), 4.06 (ddd, *J* = 10.6, 4.4 Hz, 1H), 3.77 (s, 3H), 3.66–3.61 (m, 1H), 3.53 (ddd, *J* = 10.5, 4.3, 2.0 Hz, 1H), 2.78–2.72 (m, 1H), 2.50–2.36 (m, 2H), 2.22 (app. sextet, *J* = 7.7 Hz, 1H), 2.14 (app. sextet, *J* = 7.2 Hz, 1H), 2.06 (quintet, *J* = 7.8 Hz, 2H), 1.84–1.76 (m, 1H), 1.56–1.50 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 154.3, 153.2, 132.8, 127.9, 116.1, 114.7, 81.5, 77.0, 70.0, 55.9, 48.0, 46.5, 36.2, 23.0, 20.6, 14.5, 9.3; IR (thin film) 3000, 2960, 2932, 2873, 2852, 1716, 1508 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{20}H_{28}O_4Na$ $[M + Na]^+$ 355.1885, found 355.1884.



2-60*c*

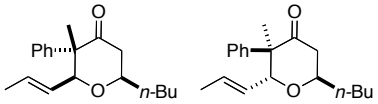
6-(Furan-2-yl)-3-methyl-3-phenyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-60*c*). Alcohol **2-28** (58 mg, 0.16 mmol) and crotonaldehyde (17 mg, 0.24 mmol) were converted to **2-60*c*** following the general procedure for THPO formation. Purification of the crude residue on a preparative TLC plate (1:9 EtOAc:hexanes) afforded THPO **2-60** as a white film in a 6.0:1.0

cis:trans ratio (29 mg, 62%). **THPO 2-60*c***: R_f = 0.44 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (app. d, *J* = 1.0 Hz, 1H), 7.37–7.32 (m, 2H), 7.31–7.27 (m, 1H), 7.20–7.18 (m, 2H), 6.40–6.39 (m, 2H), 5.50–5.43 (m, 1H), 5.17 (ddt, *J* = 15.4, 5.6, 4.9 Hz, 1H), 5.02 (dd, *J* = 12.4, 3.0 Hz, 1H), 4.59 (d, *J* = 5.5 Hz, 1H), 3.28 (dd, *J* = 15.8, 12.4 Hz, 1H), 2.71 (dd, *J* = 15.8, 3.1 Hz, 1H), 1.62 (s, 3H), 1.53 (dd, *J* = 6.5, 1.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.8, 152.7, 143.1, 139.5, 130.0, 128.4, 128.3, 127.3, 124.8, 110.5, 108.0, 84.4, 72.0, 58.8, 42.0, 18.0, 16.7; IR (thin film) 3031, 2989, 2916, 2854, 1714 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{19}H_{20}O_3Na$ $[M + Na]^+$ 319.1310, found 319.1305.



6-Butyl-3-methyl-3-phenyl-2-styryldihydro-2*H*-pyran-4(3*H*)-one (2-61). Alcohol **2-29** (36 mg, 0.10 mmol) and cinnamaldehyde (20 mg, 0.15 mmol) were converted to **2-61** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-61** as a clear colorless oil in a 8.2:1.0 *cis:trans* ratio (24 mg, 69%). A small amount of THPO **2-61*c*** and THPO **2-61*t*** was separated for characterization but most was recovered as a mixture of the two diastereomers: R_f = 0.28 (10% EtOAc/hexanes). **THPO 2-61*c***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (app. t, *J* = 7.5 Hz, 2H), 7.31–7.17 (m, 8H), 6.46 (dd, *J* = 16.1, 1.4 Hz, 1H), 5.74 (dd, *J* = 16.1, 4.4 Hz, 1H), 4.64 (dd, *J* = 4.4, 1.6 Hz, 1H), 3.99–3.93 (m, 1H), 2.71 (dd, *J* = 15.6, 11.9 Hz, 1H), 2.52 (dd, *J* = 15.6, 2.9 Hz, 1H), 1.87–1.81 (m, 1H), 1.69–1.63 (m, 1H), 1.58–1.55 (m, 1H), 1.56 (s, 3H), 1.48–1.37 (m, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9, 139.6, 136.9, 131.9, 128.6, 128.43, 128.41, 127.7, 127.4, 126.5, 124.4, 83.9, 76.9, 58.7, 44.4, 36.3, 27.6, 22.8, 16.8,

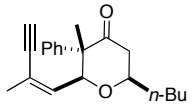
14.2; IR (thin film) 3057, 3026, 2956, 2930, 2859, 1714 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{24}H_{28}O_2Na$ $[M + Na]^+$ 371.1987, found 371.1986. **THPO 2-60*t***: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.37 (m, 6H), 7.33 (app. t, *J* = 7.4 Hz, 2H), 7.29–7.26 (m, 2H), 6.76 (d, *J* = 15.6 Hz, 1H), 6.27 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.22 (d, *J* = 8.4 Hz, 1H), 4.16 (quintet, *J* = 6.5 Hz, 1H), 2.41–2.39 (m, 2H), 1.61–1.53 (m, 1H), 1.46–1.37 (m, 1H), 1.30–1.17 (m, 7H), 0.84 (t, *J* = 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 142.4, 136.4, 136.2, 129.0, 128.8, 128.4, 127.1, 127.0, 126.9, 124.3, 80.7, 72.7, 58.2, 45.1, 35.9, 27.2, 22.7, 22.2, 14.1; IR (thin film) 3058, 3026, 2956, 2928, 2860, 1711 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{24}H_{28}O_2Na$ $[M + Na]^+$ 371.1987, found 371.1995.



2-62*c* **2-62*t***

6-Butyl-3-methyl-3-phenyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-62). Alcohol **2-29** (79 mg, 0.23 mmol) and crotonaldehyde (30 mg, 0.43 mmol) were converted to **2-62** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-62*c*** (39 mg, 60%) and **2-62*t*** (14 mg, 22%) as a clear colorless oil. **THPO 2-62*c***: R_f = 0.35 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (app. t, *J* = 7.5 Hz, 1H), 7.20–7.17 (m, 2H), 7.09 (dd, *J* = 8.3, 1.1 Hz, 2H), 5.44 (dqd, *J* = 15.4, 6.6, 1.4 Hz, 1H), 5.03 (dd, *J* = 15.5, 2.2 Hz, 1H), 4.34 (dd, *J* = 3.7, 1.2 Hz, 1H), 3.81 (ddq, *J* = 12.6, 6.6, 1.8 Hz, 1H), 2.58 (dd, *J* = 15.6, 11.9 Hz, 1H), 2.39 (dd, *J* = 15.5, 2.9 Hz, 1H), 1.73–1.67 (m, 1H), 1.57–1.51 (m, 1H), 1.49 (app. dt, *J* = 6.6, 1.4 Hz, 3H), 1.46 (s, 3H), 1.44–1.41 (m, 1H), 1.37–1.27 (m, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2, 139.8, 129.0, 128.4, 128.2, 127.1, 125.4, 84.0, 76.9, 58.6, 44.4, 36.3,

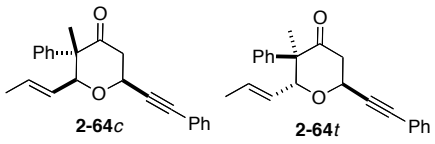
27.5, 22.8, 18.0, 16.6, 14.2; IR (thin film) 3031, 2957, 2932, 2859, 1714 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{19}H_{26}O_2Na$ $[M + Na]^+$ 309.1830, found 309.1820. **THPO 2-62*t***: R_f = 0.35 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 4H), 7.25–7.22 (m, 1H), 5.88 (dq, *J* = 17.2, 5.0 Hz, 1H), 5.60 (ddq, *J* = 14.9, 8.9, 1.9 Hz, 1H), 5.02 (d, *J* = 8.9 Hz, 1H), 4.09–4.04 (m, 1H), 2.33 (dd, *J* = 13.7, 9.8 Hz, 1H), 2.28 (dd, *J* = 13.7, 4.2 Hz, 1H), 1.75 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.54–1.49 (m, 1H), 1.41–1.33 (m, 1H), 1.28–1.21 (m, 4H), 1.19 (s, 3H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 142.8, 133.2, 128.9, 126.98, 126.95, 126.2, 81.0, 72.3, 58.0, 45.2, 36.0, 27.1, 22.7, 22.6, 18.2, 14.1; IR (thin film) 2956, 2930, 2860, 1713 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{19}H_{26}O_2Na$ $[M + Na]^+$ 309.1830, found 309.1826.



2-63*c*

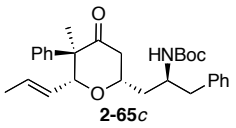
6-Butyl-3-methyl-2-((*Z*)-2-methylbut-1-en-3-ynyl)-3-phenyldihydro-2*H*-pyran-4(3*H*)-one (2-63*c*). Alcohol **2-29** (33 mg, 0.10 mmol) and 3-methylpent-2-en-4-ynal (5:1 *Z:E* ratio, 14 mg, 0.15 mmol) were converted to **2-63*c*** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-63*c*** as a clear colorless oil with a 5:1 *Z:E ratio* (14 mg, 48%): R_f = 0.35 (10% EtOAc/hexanes): ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.26–7.22 (m, 1H), 7.19–7.14 (m, 2H), 5.69 (dd, *J* = 8.7, 0.6 Hz, 1H), 4.91 (d, *J* = 8.7 Hz, 1H), 3.97–3.91 (m, 1H), 2.92 (s, 1H), 2.65 (dd, *J* = 15.8, 11.8 Hz, 1H), 2.50 (dd, *J* = 15.8, 3.2 Hz, 1H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.62 (s, 3H), 1.61–1.56 (m, 1H), 1.48–1.46 (m, 1H), 1.41–1.33 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6, 139.0, 132.1, 128.6, 128.1, 127.2, 123.4, 82.1, 81.9, 81.8,

76.9, 58.2, 44.5, 36.3, 27.4, 23.5, 22.8, 17.1, 14.2; IR (thin film) 3286, 2955, 2929, 2862, 1715 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{21}H_{26}O_2Na$ $[M + Na]^+$ 333.1830, found 333.1825.



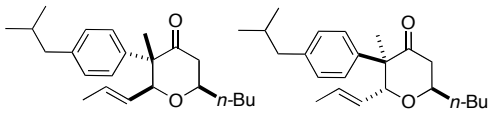
3-Methyl-3-phenyl-6-(phenylethynyl)-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-64). Alcohol **2-30** (41 mg, 0.10 mmol) and crotonaldehyde (11 mg, 0.16 mmol) were converted to **2-64** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-64** as a mixture of diastereomers (1.7:1.0 *cis:trans*) that was a clear light yellow oil (31 mg, 94%). Some of THPO **2-64***c* and THPO **2-64***t* was separated for characterization but most was recovered as a mixture of the two diastereomers: **THPO 2-64*c***: R_f = 0.44 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.48 (m, 2H), 7.37–7.33 (m, 5H), 7.30–7.28 (m, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 5.56–5.49 (m, 1H), 5.20 (dq, *J* = 15.4, 2.4 Hz, 1H), 4.92 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.49 (d, *J* = 5.5 Hz, 1H), 3.17 (dd, *J* = 15.9, 12.1 Hz, 1H), 2.79 (dd, *J* = 15.9, 3.2 Hz, 1H), 1.56 (s, 3H), 1.56 (d, *J* = 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 139.3, 132.1, 130.4, 129.0, 128.4, 128.3, 128.3, 127.4, 124.6, 122.1, 86.5, 86.3, 84.6, 67.6, 58.8, 44.6, 18.0, 16.7; IR (thin film) 2915, 1715 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{23}H_{22}O_2Na$ $[M + Na]^+$ 353.1518, found 353.1519. **THPO 2-64*t***: R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.36–7.32 (m, 5H), 7.28–7.25 (m, 3H), 5.65–5.58 (m, 1H), 5.36 (dd, *J* = 6.5, 3.3 Hz, 1H), 5.29 (ddq, *J* = 14.0, 5.4, 1.4 Hz, 1H), 5.19 (d, *J* = 6.0 Hz, 1H), 3.14 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.71 (dd, *J* = 15.0, 3.4 Hz, 1H), 1.62 (d, *J* = 6.6 Hz, 3H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 140.3, 132.0, 130.6, 129.1, 128.6, 128.5, 128.1, 127.2, 125.1,

122.0, 88.9, 86.0, 79.8, 65.2, 58.9, 43.9, 18.1, 18.0; IR (thin film) 2927, 2854, 1711 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{23}H_{22}O_2Na$ $[M + Na]^+$ 353.1518, found 353.1512.



2-65*c*

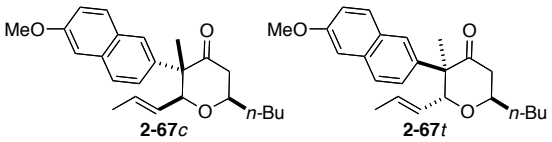
tert*-Butyl (*S*)-1-((2*S*,5*R*,6*R*)-5-methyl-4-oxo-5-phenyl-6-((*E*)-prop-1-enyl)tetrahydro-2*H*-pyran-2-yl)-3-phenylpropan-2-ylcarbamate (2-65*c*).** Alcohol **2-31** (62 mg, 0.12 mmol) and crotonaldehyde (12 mg, 0.18 mmol) were converted to **2-65c* following the general procedure for THPO formation. Purification by column chromatography (3:7 EtOAc:hexanes) of the crude residue afforded THPO **2-65***c* as a single diastereomer that was a white film (41 mg, 76%): R_f = 0.49 (30% EtOAc/hexanes); $[\alpha]^{24}_D$ = 14.1 (*c* 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.19 (m, 8H), 7.13 (app. d, *J* = 7.3 Hz, 2H), 5.55–5.48 (m, 1H), 5.06 (ddd, *J* = 15.5, 4.7, 1.6 Hz, 1H), 4.83 (d, *J* = 5.6 Hz, 1H), 4.37 (d, *J* = 4.3 Hz, 1H), 4.00–3.96 (m, 2H), 3.00–2.96 (m, 1H), 2.79 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.59 (dd, *J* = 11.8, 15.5 Hz, 1H), 2.47 (dd, *J* = 15.5, 2.0 Hz, 1H), 1.86–1.80 (m, 1H), 1.76–1.71 (m, 1H), 1.56 (d, *J* = 6.5 Hz, 3H), 1.49 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2, 155.6, 139.6, 138.0, 129.7, 129.0, 128.6, 128.32, 128.26, 127.2, 126.6, 125.2, 83.9, 79.3, 75.3, 58.4, 50.1, 44.3, 41.7, 40.1, 28.5, 18.1, 16.6; IR (thin film) 3421, 3060, 2977, 2929, 2893, 1702, 1502 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{29}H_{37}NO_4Na$ $[M + H]^+$ 486.2620, found 486.2611.



2-66*c* **2-66*t***

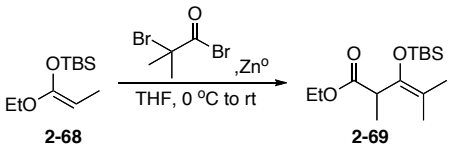
6-Butyl-3-(6-methoxynaphthalen-2-yl)-3-methyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-66). Alcohol **2-32** (48 mg, 0.12 mmol) and crotonaldehyde (13 mg, 0.18 mmol) were converted to **2-66** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-66** as a mixture of diastereomers (3.0:1.0 *cis:trans*) that was a clear light yellow oil (20 mg, 50%). Some of THPO **2-66*c*** and THPO **2-66*t*** was separated for characterization but most was recovered as a mixture of the two diastereomers. **THPO 2-66*c***: R_f = 0.60 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 5.52–5.45 (m, 1H), 5.12–5.08 (m, 1H), 4.38 (d, *J* = 4.8 Hz, 1H), 3.90–3.85 (m, 1H), 2.64 (dd, *J* = 15.5, 11.8 Hz, 1H), 2.48–2.44 (m, 3H), 1.86 (app. septet, *J* = 6.7 Hz, 1H), 1.81–1.74 (m, 1H), 1.63–1.57 (m, 1H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.51 (s, 3H), 1.51–1.35 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.90 (dd, *J* = 6.6, 1.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 140.4, 137.0, 128.9, 128.8, 128.0, 125.6, 84.1, 76.9, 58.3, 45.2, 44.5, 36.3, 30.2, 27.5, 22.8, 22.6, 22.5, 18.0, 16.7, 14.2; IR (thin film) 2955, 2929, 2867, 1714 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{23}H_{34}O_2Na$ $[M + Na]^+$ 365.2456, found 365.2453. **THPO 2-66*t***: R_f = 0.70 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 5.86 (dq, *J* = 14.0, 4.3 Hz, 1H), 5.59 (app. ddd, *J* = 15.1, 8.8, 1.1 Hz, 1H), 5.00 (d, *J* = 8.8 Hz, 1H), 4.08–4.03 (m, 1H), 2.44 (d, *J* = 7.2 Hz, 2H), 2.35 (dd, *J* = 13.6, 10.4 Hz, 1H), 2.26 (dd, *J* = 13.7, 3.5 Hz, 1H), 1.85 (app. septet, *J* = 6.7 Hz, 1H), 1.74 (d, *J* = 6.4 Hz, 3H), 1.54–1.49 (m, 1H), 1.41–1.33 (m, 2H), 1.31–1.20 (m, 3H), 1.18 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.8, 140.4, 140.1, 133.0, 129.6, 126.6, 126.3, 81.2, 72.2, 57.6, 45.1, 45.0,

36.0, 30.3, 27.1, 22.6. 22.54, 22.52, 18.2, 14.1; IR (thin film) 2955, 2927, 2868, 1713 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{23}H_{34}O_2Na$ $[M + Na]^+$ 365.2456, found 365.2447.



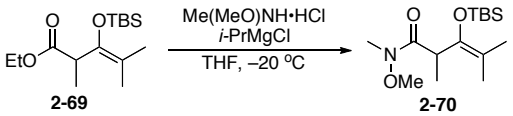
6-Butyl-3-(4-isobutylphenyl)-3-methyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-67). Alcohol **2-33** (36 mg, 0.08 mmol) and crotonaldehyde (9 mg, 0.13 mmol) were converted to **2-67** following the general procedure for THPO formation. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded THPO **2-67***c* (21 mg, 68%) and THPO **2-67***t* (8 mg, 26%) as a clear light yellow oil: **THPO 2-67*c***: R_f = 0.28 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.21 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.14–7.12 (m, 2H), 5.53 (dqd, *J* = 15.6, 6.6, 1.4 Hz, 1H), 5.12 (ddq, *J* = 15.4, 4.9, 1.7 Hz, 1H), 4.52 (dt, *J* = 3.1, 1.6 Hz, 1H), 3.96–3.90 (m, 1H), 3.92 (s, 3H), 2.69 (dd, *J* = 15.5, 11.9 Hz, 1H), 2.50 (dd, *J* = 15.6, 2.9 Hz, 1H), 1.83–1.77 (m, 1H), 1.67–1.60 (m, 1H), 1.63 (s, 3H), 1.52 (app. dt, *J* = 6.6, 1.4 Hz, 3H), 1.52–1.36 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 157.9, 135.1, 133.7, 129.7, 129.0, 128.9, 127.3, 127.0, 126.5, 125.5, 118.8, 105.6, 83.7, 77.2, 58.5, 55.5, 44.6, 36.3, 27.5, 22.8, 18.0, 16.8, 14.2; IR (thin film) 3058, 2956, 2933, 2858, 1710, 1606 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$ 389.2093, found 389.2079. **THPO 2-67*t***: R_f = 0.45 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.72 (app. t, *J* = 8.1 Hz, 2H), 7.37 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 5.92 (dq, *J* = 18.2, 4.3 Hz, 1H), 5.64 (dd, *J* = 14.9, 8.9 Hz, 1H), 5.14 (d, *J* = 8.9 Hz, 1H), 4.12–4.07 (m, 1H), 3.92 (s, 3H), 2.38–2.28 (m, 2H), 1.76 (d, *J* = 6.4 Hz, 3H), 1.55–1.48 (m, 1H), 1.39–1.30 (m,

1H), 1.26–1.18 (m, 6H), 0.93–0.87 (m, 1H), 0.84–0.81 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.7, 157.9, 137.9, 133.5, 133.2, 129.8, 129.2, 127.4, 126.3, 125.7, 125.6, 119.1, 105.5, 81.2, 72.3, 57.9, 55.5, 45.2, 36.0, 27.1, 22.7, 22.6, 18.2, 14.1; IR (thin film) 2956, 2930, 2858, 1711, 1605 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{24}H_{30}O_3Na$ [M + Na]$^+$ 389.2093, found 389.2086.



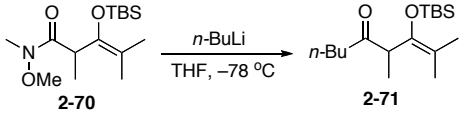
2-68 **2-69**

Ethyl 3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpent-3-enoate (2-69). 2-Bromo-2-methylpropionyl bromide (1.6 g, 6.9 mmol) was added dropwise to a suspension of activated zinc dust (0.91 g, 13.9 mmol) in THF (12 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then transferred via cannula to a solution of silyl ketene acetal **2-68** (0.5 g, 2.3 mmol) in THF (12 mL) at 0 °C. The gray-green mixture was stirred overnight, slowly warming to room temperature. The reaction mixture was then diluted with Et_2O (25 mL) and washed with H_2O (15 mL). The aqueous layer was extracted with Et_2O (20 mL x 6). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (10:1:89 Et_2O:Et_3N:hexanes) of the crude residue produced ethyl ester **2-69** as a colorless oil (0.22 g, 33%): R_f = 0.57 (10% Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15–4.03 (m, 2H), 3.53 (q, *J* = 7.3 Hz, 1H), 1.59 (s, 3H), 1.57 (s, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 142.8, 111.3, 60.7, 42.6, 26.2, 19.0, 18.9, 18.8, 14.4, 14.4, –3.5, –3.8; IR (thin film) 2956, 2932, 2905, 2859, 1736, 1675 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{30}O_3SiNa$ [M + Na]$^+$ 309.1862, found 309.1864.



2-69 2-70

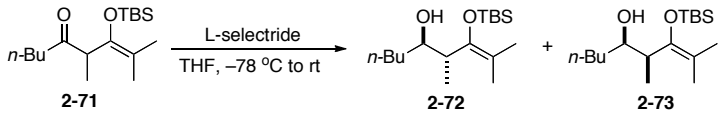
3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2,4-trimethylpent-3-enamide (2-70). A solution of 2.0 M *i*-PrMgCl (0.92 mL, 1.8 mmol) in THF was added dropwise to a solution of ethyl ester **2-69** (0.22 g, 0.77 mmol) and Me(MeO)NH•HCl (90 mg, 0.92 mmol) in THF (6.4 mL) at –78 °C. The mixture was stirred for 3.5 h at –78 °C, warmed to 0 °C, and stirred for an additional 2.5 h. A solution of 2.0 M *i*-PrMgCl (0.92 mL, 1.8 mmol) in THF and Me(MeO)NH•HCl (90 mg, 0.92 mmol) was added to the reaction mixture and stirred for 2.5 h at 0 °C. The reaction was then quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography (15:85 EtOAc:hexanes) of the crude residue afforded Weinreb amide **2-70** as a colorless oil (183 mg, 79%): R_f = 0.54 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73–3.62 (m, 1H), 3.59 (s, 3H), 3.14 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 143.7, 109.9, 77.4, 60.7, 41.1, 26.2, 18.9, 18.7, 18.6, 14.8, –3.3, –3.4; IR (thin film) 2956, 2932, 2898, 2858, 1668 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{15}H_{31}NO_3SiNa$ $[M + Na]^+$ 324.1971, found 324.1979.



2-70 2-71

3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylnon-2-en-5-one (2-71). *n*-BuLi (2.27 M in hexanes, 0.33 mL) was added dropwise to a solution of amide **2-70** (150 mg, 0.50 mmol) in THF (1.7 mL) at –78 °C. The mixture was stirred for 2.5 h and the reaction was quenched with saturated

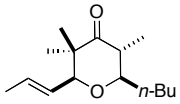
aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography (1:9 EtOAc:hexanes) of the crude residue afforded ketone **2-71** as a colorless oil (123 mg, 83%): R_f = 0.82 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (q, *J* = 7.0 Hz, 1H), 2.50 (ddd, *J* = 16.6, 8.3, 6.9 Hz, 1H), 2.36 (ddd, *J* = 16.6, 8.3, 6.6 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.56–1.45 (m, 2H), 1.27 (m, 2H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.083 (s, 3H), 0.079 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.3, 143.8, 111.7, 50.4, 40.0, 26.3, 26.2, 22.5, 19.1, 18.9, 18.7, 14.0, 13.1, –3.38, –3.42; IR (thin film) 2958, 2932, 2860, 1718, 1670 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{17}H_{34}O_2SiNa$ $[M + Na]^+$ 321.2226, found 321.2222.



2-71 **2-72** **2-73**

3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylnon-2-en-5-ol (2-72/2-73). L-Selectride (1.0 M in THF, 0.53 mL) was added dropwise to a solution of ketone **2-71** (106 mg, 0.36 mmol) in THF (3.6 mL) at –78 °C. The mixture was stirred overnight, slowly warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and the resulting solution was concentrated *in vacuo*. Purification by column chromatography (1:19 EtOAc:hexanes) of the crude residue afforded a mixture of alcohol **2-72** as a colorless oil (50 mg, 46%) and alcohol **2-73** as a colorless oil (8 mg, 8%). **Alcohol 2-72**: R_f = 0.52 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55–3.52 (m, 1H), 2.62 (app. dt, *J* = 15.7, 7.1 Hz, 1H), 2.22 (d, *J* = 2.1 Hz, 1H), 1.633 (s, 3H), 1.628 (s, 3H), 1.56–1.49 (m, 2H),

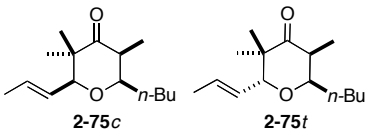
1.38–1.29 (m, 4H), 0.98 (d, J = 8.4 Hz, 3H), 0.97 (s, 9H), 0.92–0.89 (m, 3H), 0.16 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 111.9, 73.2, 41.7, 34.1, 28.0, 26.5, 23.0, 19.4, 19.2, 19.1, 15.4, 14.3, –2.7, –3.2; IR (thin film) 3567, 3489, 2957, 2932, 2859, 1713, 1668 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{17}H_{36}O_2SiNa$ $[M + Na]^+$ 323.2382, found 323.2381. **Alcohol 2-73**: R_f = 0.27 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66–3.62 (m, 1H), 2.58 (app. quintet, J = 7.0 Hz, 1H), 1.91 (br. s, 1H), 1.62 (s, 3H), 1.59 (s, 3H), 1.38–1.27 (m, 6H), 1.09 (d, J = 7.1 Hz, 3H), 0.96 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 109.2, 75.0, 41.2, 34.8, 28.4, 26.6, 22.9, 19.5, 19.3, 19.1, 14.3, 13.7, –2.4, –3.1; IR (thin film) 3340, 2956, 2930, 2858, 1708, 1669 cm^{-1}; HRMS (ES/MeOH) m / z calcd for $C_{17}H_{37}O_2Si$ $[M + H]^+$ 301.2563, found 301.2576.



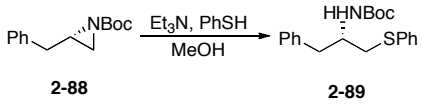
2-74

6-Butyl-3,3,5-trimethyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-74). Alcohol **2-72** (50 mg, 0.17 mmol) and crotonaldehyde (18 mg, 0.25 mmol) were converted to **2-74** following the general procedure for THPO formation. Purification by column chromatography (1:19 EtOAc:hexanes) of the crude residue afforded THPO **2-74** as a clear colorless oil (20 mg, 50%): R_f = 0.43 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dq, J = 14.1, 4.4 Hz, 1H), 5.53 (app. ddd, J = 15.3, 6.8, 1.4 Hz, 1H), 3.64 (d, J = 7.0 Hz, 1H), 3.23–3.19 (m, 1H), 2.64–2.61 (m, 1H), 1.75 (d, J = 6.5 Hz, 3H), 1.72–1.67 (m, 1H), 1.60–1.52 (m, 1H), 1.43–1.25 (m, 4H), 1.11 (s, 3H), 0.97–0.93 (m, 6H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.8, 130.3, 126.3, 85.3, 83.0, 49.3, 45.5, 33.9, 27.1, 22.9, 20.0, 19.7, 18.2, 14.2, 9.9; IR (thin

film) 2959, 2934, 2859, 1710 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{30}O_2N$ $[M + NH_4]^+$ 256.2277, found 256.2276.



6-Butyl-3,3,5-trimethyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2-75). Alcohol **2-73** (9 mg, 0.03 mmol) and crotonaldehyde (6 mg, 0.09 mmol) were converted to **2-75** following the general procedure for THPO formation using 3.0 equiv of aldehyde and 3.0 equiv of BF_3•OEt_2 instead of 1.5 equiv. The solution was run at 0.3 M instead of 1.0 M. Purification by column chromatography (1:19 EtOAc:hexanes) of the crude residue afforded THPO **2-75** as a mixture of diastereomers (1.0:1.8 *cis:trans*) that was a clear colorless oil (5.2 mg, 73%). Some of the THPO **2-75*t*** was separated for characterization but most of it was recovered as a mixture of the two diastereomers. **THPO 2-75*c***: R_f = 0.49 (5% EtOAc/hexanes); ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.9, 130.4, 126.5, 85.6, 79.0, 49.3, 47.5, 31.6, 27.9, 22.8, 21.1, 21.0, 18.2, 14.2, 12.6; ^{13}C chemical shifts were determined by taking an ^{13}C NMR spectra of the diastereomeric mixture and subtracting peaks that belonged to THPO **2-75*t***. **THPO 2-75*t***: R_f = 0.42 (5% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (dq, *J* = 18.4, 4.3 Hz, 1H), 5.54 (dd, *J* = 15.3, 7.5 Hz, 1H), 4.18–4.10 (m, 1H), 3.79 (d, *J* = 7.4 Hz, 1H), 3.23 (app. quintet, *J* = 6.8 Hz, 1H), 1.75 (d, *J* = 6.4 Hz, 3H), 1.39–1.27 (m, 4H), 1.17 (s, 3H), 0.93 (s, 3H), 0.90 (d, *J* = 7.5 Hz, 3H), 0.88–0.83 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.0, 130.6, 126.5, 79.2, 78.6, 44.5, 29.8, 27.4, 26.0, 22.6, 20.7, 19.7, 18.1, 14.2, 10.3; IR (thin film) 2959, 2932, 2859, 1709 cm^{-1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{15}H_{30}O_2N$ $[M + NH_4]^+$ 256.2277, found 256.2274.



2-88 **2-89**

(*S*)-*tert*-butyl 1-phenyl-3-(phenylthio)propan-2-ylcarbamate (2-89). Thiophenol (0.3 mL, 2.8 mmol) was added to a solution of aziridine **2-88**[43] (440 mg, 1.89 mmol) and triethylamine (0.5 mL, 3.8 mmol) in 6.3 mL of MeOH. After 24 h the mixture was concentrated *in vacuo* and purified by column chromatography (1:19 EtOAc:hexanes) to afford **2-89** as a white solid (524 mg, 80%): R_f = 0.27 (5% EtOAc/hexanes); $[\alpha]^{24}_{D}$ = 19.0 (*c* 2.85, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.16 (m, 10H), 4.69 (br. s, 1H), 4.06 (br. s, 1H), 3.08–2.98 (m, 2H), 2.96–2.86 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 137.6, 136.2, 129.7, 129.5, 129.1, 128.6, 126.7, 126.4, 79.5, 51.4, 39.5, 37.8, 28.4; IR (thin film) 3352, 3061, 2977, 1714, 1694 cm ^{1}; HRMS (ES/MeOH) *m* / *z* calcd for $C_{20}H_{25}NO_2SNa$ $[M + Na]^+$ 366.1504, found 366.1505.

References

[1] (a) Smith, A. B.; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675–687. (b) Wender, P. A.; Loy, B. A.; Schrier, A. J. *Isr. J. Chem.* **2011**, *51*, 453–472. (c) Yeung, K.-S., Paterson, I. *Chem. Rev.* **2005**, *105*, 4237–4313.

[2] Catelani, G.; Monti, L.; Ugazio, M. *J. Org. Chem.* **1980**, *45*, 919–920.

[3] (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231551 [A2960910], 1996; *Chem. Abstr.* **1997**, *126*, 6553. (b) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231552, 1996; *Chem. Abstr.* **1996**, *125*, 326518. (c) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 323–328.

[4] Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015–6016.

[5] Pavan, M.; Bo, G. *Physiol. Comp. Oecol.* **1953**, *3*, 307–312.

[6] (a) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951–1954. (b) Pettit, G. R.; Xu, J. P.; Chapuis, J. C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149–1152.

[7] For reviews on tetrahydropyran synthesis: (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053. (b) Larrosa, I.; Romea, P.; Urpi, F. *Tetrahedron* **2008**, *64*, 2683–2723. (c) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445. (d) Perry, M. A.; Rychnovsky, S. D.; Sizemore, N. Synthesis of Saturated Tetrahydropyrans. In *Synthesis of Saturated Oxygenated Heterocycles*; Cossy, J., Ed.; Topics in Heterocyclic Chemistry Series; Springer-Verlag: Berlin, 2014.

[8] Das, S.; Li, L.-S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 123–126.

[9] (a) Johannsen, M.; Jorgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757–5762. (b) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405. (c) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398–2400. (d) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974–9983. (e) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2664–2668.

[10] (a) Japp, F. R.; Maitland, W. *J. Chem. Soc.,* **1904***, 85*, 1473–1489. (b) Clarke, P. A.; Martin, W. H. C. *Org. Lett.* **2002**, *4*, 4527–4529. (c) Clarke, P. A.; Martin, W. H. C. *Tetrahedron* **2005**, *61,* 5433–5438.

[11] (a) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218–1228. (b) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880–2883. (c) Athe, S.; Chandrasekhar, B.; Roy, S.; Pradhan, T. K.; Ghosh, S. *J. Org. Chem.* **2012**, *77*, 9840–9845. (d) Yao, H.; Ren, J.; Tong, R. *Chem. Commun.* **2013**, *49*, 193–195.

[12] (a) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141–144. (b) Smith A. B.; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909–912. (c) Smith, A. B.; Minbiole, K. P.; Verkoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913–916.

[13] (a) Tay, G. C.; Gesinski, M. R.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 4536–4539. (b) Tay, G. C.; Huang, C. Y.; Rychnovsky, S. D. *J. Org. Chem.* **2014**, *79*, 8733–8749.

[14] (a) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567–4571. (b) Sun, C.; Zhang, Y.; Xiao, P.; Li, H.; Sun, X.; Song, Z. *Org. Lett.* **2014**, *16*, 984–987.

[15] (a) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662–15663. (b) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1589–1591.

[16] Cockerill, G. S.; Kocienski, P. J. *Chem. Soc., Perkin Trans. 1* **1985**, 2093–2100.

[17] Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1113–1116.

[18] Bond and hash bonds are used to represent relative stereochemistry on racemic compounds. Wedged bonds (bold and hashed) are used to show stereochemistry on enantiomerically enriched compounds. Maehr, H. *J. Chem. Educ.* **1985**, *62*, 114–120.

[19] For a recent review on Prins cyclization: Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316–8326.

[20] Wenzel A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217.

[21] Williams, J. M.; Jobsen, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

[22] Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, *14*, 1297–1300.

[23] (a) Smith, W. C.; Norton, D. G. *Organic Syntheses;* Wiley: New York, 1963; Collect. Vol. IV, pp 348–350. (b) Baigrei, L. M.; Lenoir, D.; Seikaly, H. R.; Tidwell, T. T. *J. Org. Chem.* **1985**, *50*, 2105–2109.

[24] The desilyated product of **2-22** as well as alkylated *tert*-butyldimethylsilane was observed by ^{1}H NMR spectroscopy.

[25] (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P. Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926. (b) Tamura, S.; Ohno, T.; Hattori, Y.; Murakami, N. *Tetrahedron Lett.* **2010**, *51*, 1523–1525.

[26] Malathong, V.; Rychnovsky, S. D. *Org. Lett.* **2009**, *11*, 4220–4223.

[27] (a) Chem, K.-M.; Hardtman, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahdron Lett.* **1987**, *28*, 155–158. (b) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233–2238.

[28] Tillman A. L.; Dixon, D. J. *Org. Biomol. Chem.* **2007**, *5*, 606–609.

[29] Leardi, R. *Anal. Chem. Acta* **2009**, *652*, 161–172.

[30] Gribble, G. W.; Jiang, J.; Liu, Y. *J. Org. Chem.*, **2002**, *67*, 1001–1003.

[31] Both TMSOTf and $BF_3{\cdot}OEt_2$ separately were used as the Lewis acid with indole carboxaldehyde, but the cyclizations were unsuccessful.

[32] Enantiomeric ratios for compounds **2-54** and **2-49** were measured by HPLC on a Chiralcel AD column using 5% *i*-PrOH/*n*-hexane (**2-54**) or 10% *i*-PrOH/*n*-hexane (**2-49**). Details are provided in the Appendix.

[33] On a 0.17 mmol (50 mg) scale, the yield was 77%

[34] Boehn, E. E.; Thaller, V.; Whiting, M. C. *J. Chem. Soc.* **1963**, 2535–2540.

[35] THPO **2-61***c* was isolated as a single diastereomer and resubjected to the cyclization conditions (1.0 M CH_2Cl_2, 1.5 equiv $BF_3{\bullet}OEt_2$, –78 °C for 4 hours), no isomerization to THPO **2-61***t* was observed by H^1 NMR analysis.

[36] (a) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 850–858. (b) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859–864.

[37] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

[38] See THPO products **18**, **19** and **23** in reference 15a.

[39] Duffy, J. L.; Yoon, T. P.; Evans, D. A. *Tetrahedron Lett.* **1995**, *36*, 9245–9248.

[40] The preferred conformations of the tetrahydropyranones **2-74**, **2-75***c* and **2-75***t* were calculated using B3LYP/6-31G(d) using Spartan '14. The calculations were carried out in a vacuum and the energies were evaluated at 273.15 K. Details are included in the Appendix.

[41] Kenworthy, M. N.; Kilburn, J. P.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 19–22.

[42] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J.; *Organometallics* **1996**, *15*, 1518–1520.

[43] (a) Braga, A. L.; Paixao, M. W.; Ludtke, D. S.; Silveira, C. C.; Rodrigues, O. E. D. *Org. Lett.* **2003**, *5*, 2635–2638. (b) Braga, A. L.; Schneider, P. H.; Paixao, M. W.; Deobald, A. M.; Peppe, C.; Bottega, D. P. *J. Org. Chem.* **2006**, *71*, 4305–4307.

Chapter 3

Synthesis of Quinolizidine and Indolizidine Heterocycles Using Intramolecular Aza-Diels–Alder Reactions

Abstract: The scope and diastereoselectivity of an intramolecular aza-Diels–Alder reaction starting from a variety of 2-cyano-1-aza-1,3-butadienes was explored. The key reactions involved in synthesizing the Diels–Alder precursors are an imine condensation and a Strecker reaction and subsequent oxidation. The method provides a route for the synthesis of substituted quinolizidine and indolizidine heterocycles containing a cyanoenamine functional group.

Introduction

Indolizidines and quinolizidines are a common motif in numerous alkaloid natural products (Figure 3-1).[1] These saturated hetrocyclic systems and their derivatives offer an organized site for specific biological binding.[2]

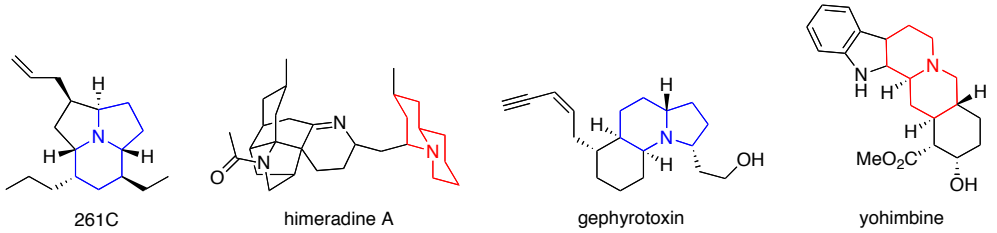


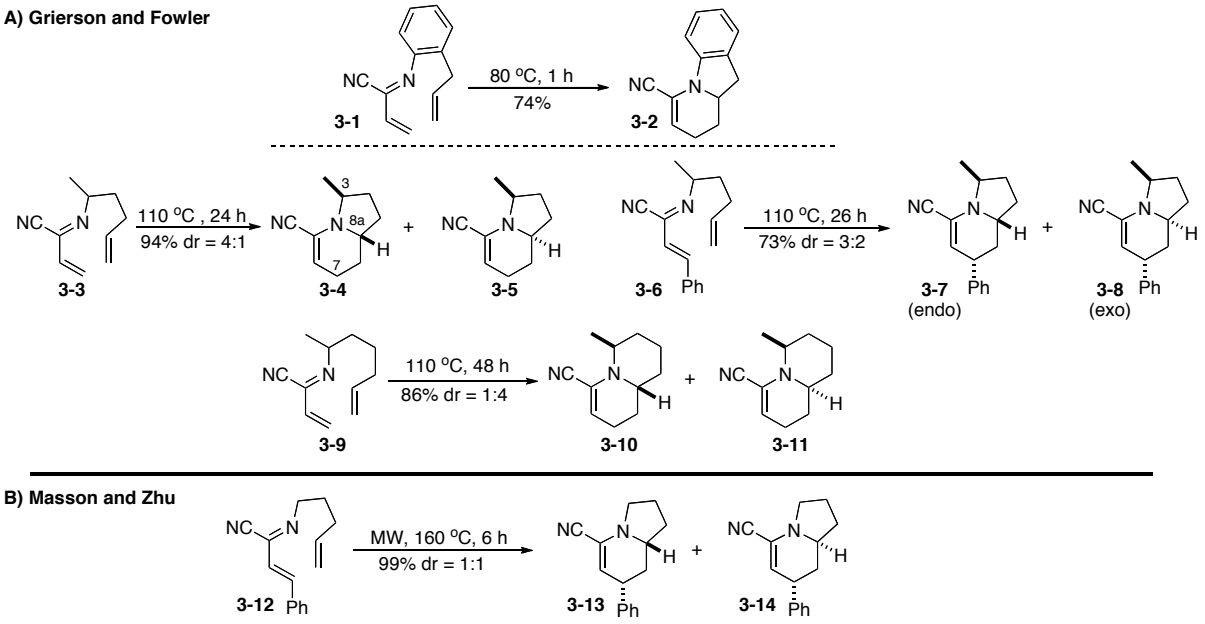
Figure 3-1. Natural products containing indolizidine (blue) and quinolizidine (red) heterocycles such as 261C,[3] himeradine A,[4] gephyrotoxin,[5] and yohimbine[6]

A variety of indolizidine and quinolizidine heterocycle syntheses via a Diels–Alder cyclization have been reported.[7] Despite these numerous reports, the Diels–Alder reaction with cyano-azadienes is still an underdeveloped strategy for the synthesis of nitrile-substituted indolizidines and quinolizidines.[8] The resulting cyanoenamine derivatives provide a versatile functional handle for future manipulations without the use of protecting groups or additional synthetic operations.[9] This chapter presents the scope and diastereocontrol of the aza-Diels–Alder cyclization with 2-cyano-1-aza-1,3-butadienes for the synthesis of indolizidine and quinolizidine heterocycles.

A few synthetic methods focused on the preparation of indolizidines and quinolizidines with cyano-azadienes have been reported.[10–17] In 1991, Fowler and Grierson reported the cyclization of aniline-derived indolizidines (Scheme 3-1 A).[11] A subsequent report revealed that alkyl substrates are less reactive and require higher temperatures and longer reaction times.[12] The diastereomeric preference of the 3,8a-*cis* to 3,8a-*trans* relationship between the bridgehead proton (shown) and the methyl group resulted from either a predominantly *endo*-pathway, as with **3-3** and **3-6**, or a predominantly *exo*-pathway as with **3-9**. Fowler and Grierson examined

three different substrates, but because of the small substrate scope, they did not report a trend in the diastereoselectivity of this transformation. More recently, Masson and Zhu reported a one-pot condensation/oxidation cyanation to afford *N*-homoallyl-derived substrates.[17] They employed homoallyl-derived substrate **3-12** in an aza-Diels–Alder cyclization to obtain the requisite indolizidine in 99% yield and a 1:1 diastereomeric ratio (Scheme 3-1 B). Due to the limited substrates studied for this transformation, we wanted to further explore the diastereoselectivity of this reaction, particularly with respect to substitution on the dienophile.

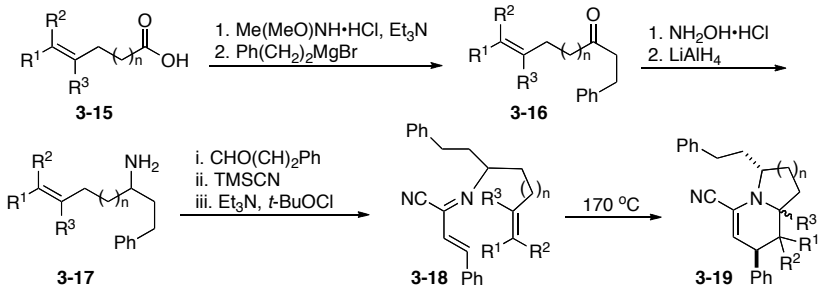
Scheme 3-1. Examples of aza-Diels–Alder cyclization from a cyano-azadiene to form indolizidine and quinolizidine heterocycles



An overview of the synthetic rounte discussed in this chapter is shown in Scheme 3-2. The synthesis began with Weinreb amide formation and nucleophilic addition of phenethylmagnesium bromide to produce ketone **3-16**. Condensation of ketone **3-16** with hydroxylamine hydrochloride followed by reduction afforded amine **3-17**. A three step, one pot condensation, cyanation, oxidation sequence resulted in Diels–Alder precursor **3-18**. The desired indolizidine/quinolizidine (**3-19**) was obtained following a thermal aza-Diels–Alder cyclization.

This method allows for the formation of substituted indolizidine and quinolizidine heterocycles and provides a system in which to study the effect of dienophile substitution on diastereoselectivity.

Scheme 3-2. General overview of this aza-Diels–Alder method



Dr. Nicholas Sizemore (King's College, formerly Rychnovsky group graduate student) designed the substrate scope for this project and completed the synthesis of intermediate **3-17**.[18] The tether length was varied to obtain either indolizidines (n = 1) or quinolizidines (n = 2). The dienophile substitution (R^1, R^2, and R^3) was varied to study the efficiency and selectivity of the cyclization. In order to reduce the volatility of the substrates in the sequence and provide a UV active chromophore for reaction monitoring, a phenethyl side change was included α to the nitrogen.

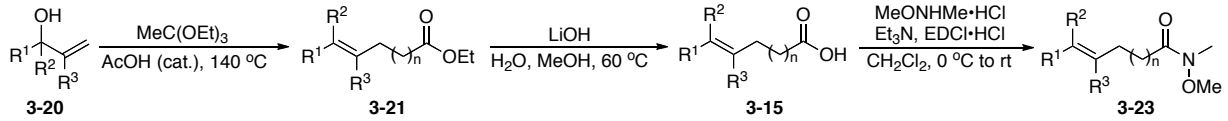
Results and Discussion

*Synthesis of Intermediate **3-17***[19]

The synthesis of substituted alkenes **3-23**c–e began with a Johnson orthoester Claisen rearrangement of the corresponding commercially available allylic alcohols **3-20**c–e (Table 3-1) to afford esters **3-21**c–e.[20] Hydrolysis of esters **3-21**c–e with lithium hydroxide resulted in carboxylic acids **3-15**c–e. Commercially available 4-pentenoic acid (**3-15**a), 5-hexenoic acid (**3-15**b), and crude carboxylic acids **3-15**c-e underwent Weinreb amide formation under standard conditions with *N,O*-dimethylhydroxylamine hydrochloride, in the presence of triethylamine and

N-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride to furnish desired amides **3-23**a–e.

Table 3-1. Synthesis of Weinreb amide **3-23**

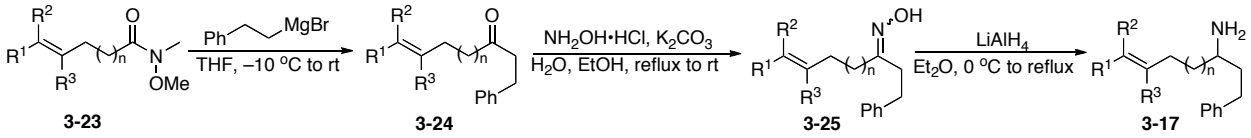


3-20 **3-21** **3-15** **3-23**

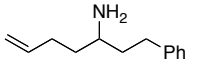
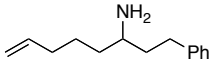
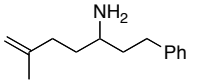
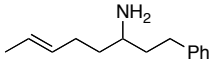
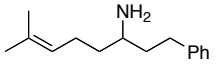
starting material	R^1	R^2	R^3	n	Claisen rearrangement	hydrolysis and amide formation	product
3-15a	H	H	H	1	--	42%	**3-23**a
3-15b	H	H	H	2	--	quant.	**3-23**b
3-20c	H	H	Me	1	69%	48%	**3-23**c
3-20d	Me	H	H	1	68%	53%	**3-23**d
3-20e	Me	Me	H	1	33%	36%	**3-23**e

Weinreb amide **3-23** was then treated with freshly prepared phenethylmagnesium bromide to afford ketone **3-24** (Table 3-2).[21,22] Condensation of the ketone with hydroxylamine hydrochloride in the presence of potassium carbonate was high yielding and led to oxime **3-25** as an inconsequential 1:1 mixture of *E*:*Z* isomers. Oxime **3-25** was reduced with lithium aluminum hydride to furnish amine **3-17**. This route provided a useful strategy for the synthesis of the substituted dienophile amine precursor. Although some of the steps in the sequence to amines **3-17**a–e were low yielding due to volatility of the starting materials and products, Sizemore was able to obtain gram quantities of the desired amines.

Table 3-2. Preparation of amine **3-17**



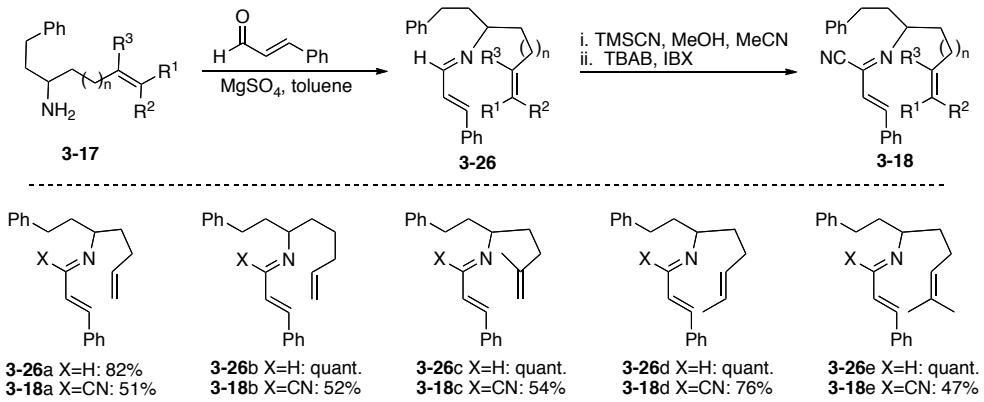
3-23 **3-24** **3-25** **3-17**

R^1	R^2	R^3	n	nucleophilic addition	condensation	reduction	product
H	H	H	1	85%	quant.	92%	 **3-17**a
H	H	H	2	56%	quant.	90%	 **3-17**b
H	H	Me	1	68%	quant.	98%	 **3-17**c
Me	H	H	1	81%	89%	94%	 **3-17**d
Me	Me	H	1	41%	99%	76%	 **3-17**e

Synthesis of the Cyclization Precursor **3-18**

With amines **3-17**a–e in hand, different strategies to access cyano-azadiene **3-18** were investigated. Sizemore had followed Masson and Zhu's one pot protocol consisting of imine condensation/oxidation cyanation. The yields were significantly lower than expected and not reproducible.[17] A modified two-pot procedure was then explored with isolation of the intermediate imines **3-26**a–e (Scheme 3-3). Treatment of amines **3-17**a–e with *trans*-cinnamaldehyde in the presence of $MgSO_4$ for twelve hours afforded desired imines **3-26**a–e in good yields. Imines **3-26**a–e were pretreated with trimethylsilyl cyanide and a stoichiometric amount of methanol to initiate the Strecker reaction.[23] Subsequent oxidation with tetrabutylammonium bromide and 2-iodoxybenzoic acid furnished desired Diels–Alder precursors **3-18**a–e in modest yields.

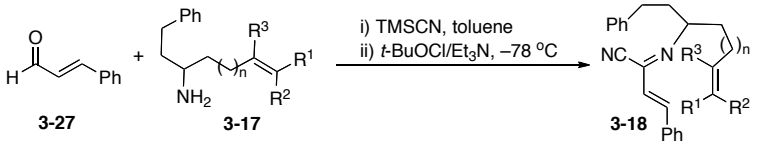
Scheme 3-3. First generation synthesis of the Diels–Alder precursors starting from amine **3-17**



Further optimization was performed to obtain higher yields of the Diels–Alder precursor. Masson and Zhu reported[17] that bulker amines slowed down the reaction rate significantly; in these cases, addition of catalytic quantities of iodine led to higher conversion. Addition of catalytic amounts of I_2 to the Strecker/oxidization of imine **3-26**b led to a 9% increase in yield. Because of the reversibility of the Strecker reaction and the sensitivity of the resulting product, the reaction could not be monitored by thin-layer chromatography. The one pot condensation, cyanation, and oxidation sequence on amine **3-17**b was monitored via ^{1}H NMR spectroscopy in d_8-toluene and it was found that the condensation and cyanation steps went to full conversion; therefore, the oxidation step was the yield-determining step. To optimize this step, other oxidants were then examined to replace IBX. A more recent report from Zhu reported the use of oxone and TBAB in a one-pot oxidation three-component Strecker reaction.[24] When **2-26**b was subjected to oxone instead of IBX, the yield remained consistently low (34%). Instead of direct oxidation of the amine after cyanation, *N*-chlorination of the resulting amine followed by dehydrochlorination was explored to yield **3-18**b.[25,26] Halogenation with *N*-chlorosuccinimide followed by elimination with potassium hydroxide led to a low yield. Treatment of the cyanation intermediate with *tert*-butyl hypochlorite and triethylamine resulted in much higher yields

(Table 3-3). Optimized procedures for the one-pot formation of Diels–Alder precursors **3-18**a–e began with condensation of amines **3-17**a–e with *trans*-cinnamaldehyde (**3-27**) followed by cyanation with TMSCN, *N*-chlorination with *tert*-butyl hypochlorite, and dehydrochlorination to afford desired intermediate **3-18**a–e.

Table 3-3. Second generation synthesis of the Diels–Alder precursors starting from amine **3-17**



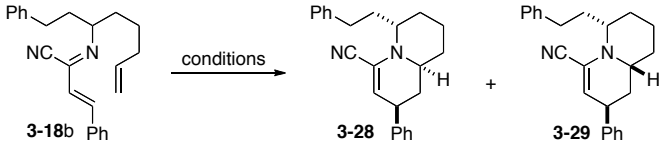
3-27 **3-17** **3-18**

entry	R^1	R^2	R^3	n	product	yield (%)
1	H	H	H	1	**3-18**a	86
2	H	H	H	2	**3-18**b	80
3	H	H	Me	1	**3-18**c	75
4	Me	H	H	1	**3-18**d	74
5	Me	Me	H	1	**3-18**e	67

Diels–Alder Cyclization

With cyano-azadienes **3-18**a–e in hand, the Diels–Alder reaction was optimized with cyano-azadiene **3-18**b. By ^{1}H NMR spectroscopy analysis, the starting material **3-18**b was consumed after 21 h at 180 °C (entry 4). The diastereomeric ratio was 1:2 of compounds **3-28** to **3-29**, this ratio was seen in most cases examined. The product is thermally stable at 180 °C and prolonged heating of the reaction mixture does not lead to significant decomposition of the product (entry 5). Higher temperatures led to quick decomposition of the starting material and possibly product (entry 6). There was no reaction observed at 150 °C (entry 13) and at 160 °C, starting material decomposition occurred faster than formation of product (entry 12). There were no observable differences for heating the reaction mixture with a microwave reactor or thermally (entry 8 and 10). Trace amounts of water helped promote the Diels–Alder cyclization, dry solvent lowered the yield (entry 10 and 14). Solvents of varying polarity were examined (entry 14–20) and toluene was determined to be the solvent of choice. There were no effects of reaction

Table 3-4. Optimization of the Diels–Alder reaction with cyano-azadienes **3-18**b



entry	temp (°C)	time	solvent	Conc (M)	additive	% yield[d]
1	180[a]	2 h	wet toluene[c]	0.04	-	24
2	180[a]	5 h	wet toluene[c]	0.04	-	38
3	180[a]	13 h	wet toluene[c]	0.04	-	53
4	180[a]	21 h	wet toluene[c]	0.04	-	64
5	180[a]	29 h	wet toluene[c]	0.04	-	61
6	220[a]	15 min	wet toluene[c]	0.04	-	30
7	170[a]	8 h	wet toluene[c]	0.04	-	59
8	170[a]	23 h	wet toluene[c]	0.04	-	64
9	170[a]	31 h	wet toluene[c]	0.04	-	62
10	170[b]	24 h	wet toluene[c]	0.04	-	62
11	160[a]	8 h	wet toluene[c]	0.04	-	38
12	160[a]	24 h	wet toluene[c]	0.04	-	59
13	150[a]	24 h	wet toluene[c]	0.04	-	no rxn
14	170[b]	24 h	dry toluene	0.04	-	48
15	170[b]	24 h	*p*-xylene	0.04	-	12
16	170[b]	24 h	chlorobenzene	0.04	-	decomp
17	170[b]	24 h	diglyme	0.04	-	decomp
18	170[b]	24 h	ethylene glycol	0.04	-	decomp
19	170[b]	24 h	pyridine	0.04	-	37
20	170[b]	24 h	water	0.04	-	decomp
21	170[b]	24 h	wet toluene[c]	0.02	-	62
22	170[b]	24 h	wet toluene[c]	0.01	-	59
23	170[b]	24 h	wet toluene[c]	0.04	BHT	23
24	170[b]	24 h	wet toluene[c]	0.04	TMSOK	47
25	170[b]	24 h	wet toluene[c]	0.04	Al_2O_3	66
26	170[b]	24 h	wet toluene[c]	0.04	Bu_3SnH	40
27	170[b]	24 h	wet toluene[c]	0.04	SiO_2	27
28	170[b]	24 h	wet toluene[c]	0.04	DBU	decomp
29	170[b]	24 h	wet toluene[c]	0.04	H_3PO_4	24
30	rt to 100[b]	24 h	wet toluene[c]	0.04	$AlCl_3$	no rxn to decomp
31	rt to 100[b]	24 h	wet toluene[c]	0.04	$Sc(OTf)_3$	no rxn to decomp
32	rt to 100[b]	24 h	wet toluene[c]	0.04	IPrCuOTf	no rxn
33	rt to 50[b]	24 h	wet toluene[c]	0.04	IPrAuOTf	no rxn
34	100[b]	24 h	wet toluene[c]	0.04	IPrAuOTf (30 mol%)	28

[a]Heating with microwave. [b]Heating thermally. [c]The toluene was stored over water [d]Yields were determined by ^{1}H NMR spectroscopy with respect to mesitylene as internal standard.

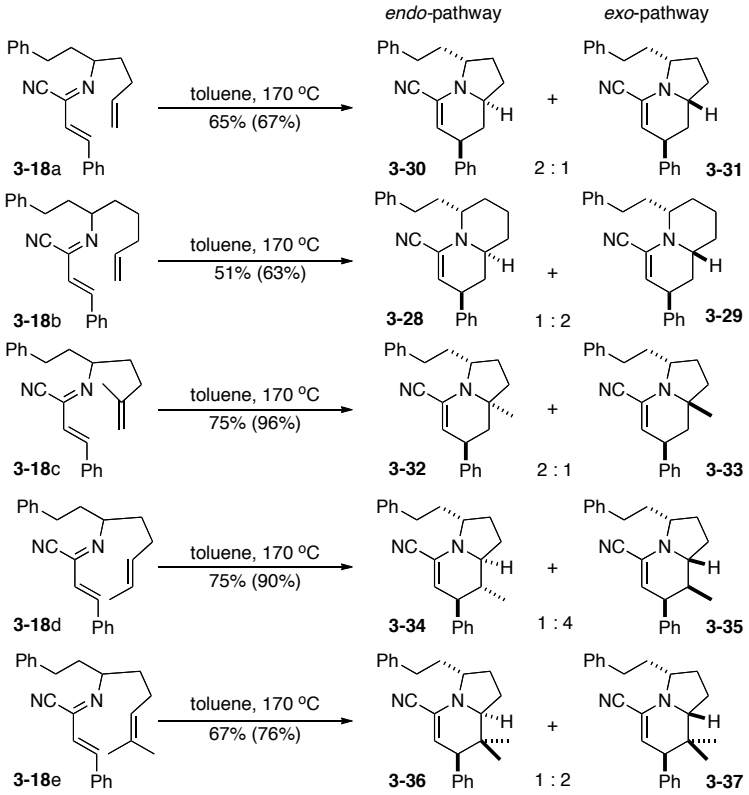
concentrations on the yield of the reaction (entry 10, 21, and 22). A variety of additives were tested to promote the cyclization or to suppress possible side reactions (entry 23–34), but the highest reproducible yield was achieved with no additives. The IPrAuOTf was generated in situ from a 1:1 mole ratio of IPrAuCl and AgOTf and promoted the cyclization at a lower temperature (entry 34). Unfortunately it seemed that stoiometric amounts of the gold additive

were required; thirty mole percent of the gold was used and only thirty percent of the product was obtained. After optimization, the Diels–Alder cycloaddition of cyano-azadienes **3-18**a–e were conducted at 170 ºC in 0.04 M wet toluene.

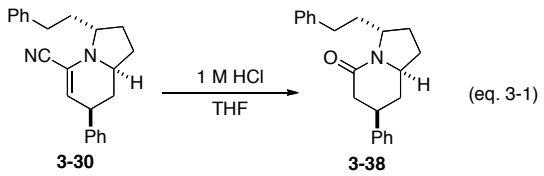
The Diels–Alder reaction with cyano-azadienes **3-18**a and **3-18**c-e afforded the corresponding indolizidines as a mixture of two diastereomers (Scheme 3-4). Because of the presence of the stereocenter on **3-18**a–e, there are four possible diastereomeric products, two arising from *exo*-transition states and two arising from through *endo*-transition states. In all cases examined in this study, only two diastereomers were observed. The stereochemistry of **3-30** was determined by hydrolysis of the cyanoenamine to the amide (eq. 3-1). The NOE correlations of amide **3-38** reveal a *cis*-relationship between the substituents on the pyrrolidine ring.[27] The NOE correlations also clearly indicate an *endo*-oriented cyclization with respect to the tether, resulting in a *cis*-relationship between the substituents on the piperidine phenyl substituent and the tether. The minor diastereomer arose from an *exo*-oriented cyclization. This selectivity matches a similar substrate from Grierson and Fowler's report (Scheme 3-1, compound **3-6**).[12] Extension of the tether length by one carbon resulted in a reversal in cyclization orientation (compound **3-18**b). In this case the major diastereomer arose from an *exo*-oriented cyclization instead of an *endo*-pathway. Again, Grierson and Fowler observed this reversal in selectivity when forming quinolizidines (Scheme 3-1, compound **3-9**). Cyclization of **3-18**c afforded a 2:1 ratio of diastereomers in a 75% yield. The stereochemical bias of the Diels–Alder cycloaddition pathway was unchanged when substitution was added onto the internal position of the dienophile (cyano-azadiene **3-18**c); the diastereoselectivity of the reaction was similarly *endo*-selective as was observed for **3-18**a. The NOE correlations, of indolizidine **3-32** reveal a *cis*-relationship between the substituents on the pyrrolidine ring and a *cis*-relationship between the substituents

on the piperidine phenyl substituent and the tether. *E*-alkene **3-18**d underwent the cyclization to give indolizidines **3-34** and **3-35** in a 75% yield as a 1:4 ratio. The Diels–Alder reaction with **3-18**e afforded indolizidines **3-36** and **3-37** in a 1:2 ratio of diastereomers in a 67% yield. The major products of compounds **3-18**d and **3-18**e with substitution on the terminal position of the dienophile resulted from an *exo*-oriented cyclization. Cyclization of substrate **3-18**c generated a fully substituted carbon and cyclization of cyano-azadiene **3-18**e furnished a quaternary center. The stereochemistry of the dienophile for **3-18**c and **3-18**d was transferred to the product, suggesting that the cyclization occurred in a concerted manner rather than a step-wise ionic or a di-radical pathway.

Scheme 3-4. Aza-Diels–Alder cyclizations[a]



[a]Values in parentheses represent yields determined by ^{1}H NMR spectroscopy with respect to mesitylene as internal standard.



Future Directions

In collaboration with the Sizemore group at King's college, computational studies have been initiated to better understand the origins of the observed diastereoselectivities for this class of Diels–Alder cycloadditions. Further studies on the reactivity of the versatile cyanoenamine functional group on the resulting indolizidine and quinolizidine heterocycles could allow for late stage manipulations for the synthesis of a variety of indolizidine and quinolizidine containing natural products.

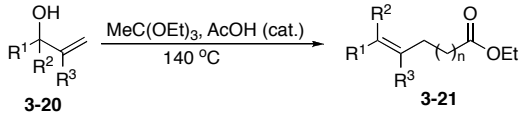
Conclusion

The aza-Diels–Alder cycloaddition with cyano-azadienes has been developed to synthesize cyanoenamine containing indolizidine and quinolizidine heterocycles. The approach to construct these heterocycles has proven a viable synthetic strategy beyond simple, unsubstituted cases. Formation of indolizidines with an unsubstituted dienophile or substitution at the internal position of the dienophile primarily underwent an *endo*-pathway. The major products of an extended tether or substitution at the external position on the dienophile arose primarily from an *exo*-oriented cyclization. This study provides a better understanding of the effect of tether length and dienophile substitution on diastereoselectivity of the aza-Diels–Alder cycloaddition.

Experimental Section

General Information. Unless otherwise stated, reactions were carried out in flame- or oven-dried glassware under an atmosphere of Ar. When specified, glassware was washed with 0.5 M ethanolic HCl, then 0.5 M ethanolic KOH. All commercially available reagents were used as received unless stated otherwise. TMSCN was distilled neat under an argon atmosphere. Solvents, such as CH_2Cl_2, Et_2O, THF, MeCN and toluene were purchased as HPLC-grade and passed though a solvent purification system equipped with activated alumina columns. Thin layer chromatography (TLC) was carried out using glass plates coated with a 250 μm layer of 60 Å silica gel. TLC plates were visualized with a UV lamp at 254 nm, or by staining with *p*-anisaldehyde, potassium permanganate, phosphomolybdic acid, or vanillin. Flash column chromatography was performed using 40–63 μm silica gel.

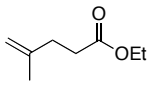
^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 126 MHz. Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, app. = apparent, br. = broad), coupling constant(s) in hertz (Hz), and integration. Infrared spectra were recorded on NaCl plates. High-resolution mass spectrometry was performed using ESI-TOF.



3-20 **3-21**

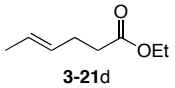
General Procedure to Form Ester 3-21 via a Johnson Ortho-Ester Claisen Rearrangement:

To a dry Ar-flushed microwave vial was added appropriate alcohol **3-20** (42.1 mmol, 1.00 equiv), triethylorthoacetate (62.7 mmol, 1.49 equiv) and AcOH (1.25 mmol, 0.03 equiv). The vial was then capped and heated thermally at 140 °C until starting material was consumed. The reaction mixture was then cooled to rt, partitioned between Et_2O (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with Et_2O (3 **x** 5 mL). The combined organic layers were stirred with 1 M aq. HCl (10 mL) at rt for 30 min, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.



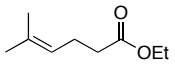
3-21c

Ethyl 4-methylpent-4-enoate (3-21c). 2-Methyl-2-propen-1-ol (**3-20**c, 3.55 mL, 42.1 mmol) was converted to **3-21**c following the general procedure for ester formation to afford a clear yellow oil (4.16 g, 69%): R_f = 0.31 (5% EtOAc/hexanes). Spectral data matched those reported in the literature.[28]



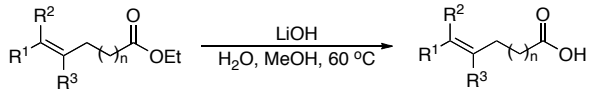
3-21d

(*E*)-Ethyl hex-4-enoate (3-21d). 3-Buten-2-ol (**3-20**d, 3.65 mL, 42.1 mmol) was converted to **3-21**d following the general procedure for ester formation to afford a clear yellow oil (4.08 g, 68%): R_f = 0.28 (5% EtOAc/hexanes). Spectral data matched those reported in the literature.[29]



3-21e

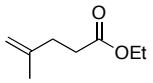
Ethyl 5-methylhex-4-enoate (3-21e). 2-Methyl-3-buten-2-ol (**3-20**e, 4.40 mL, 42.1 mmol) was converted to **3-21**e following the general procedure for ester formation to afford a clear yellow oil (2.18 g, 33%): R_f = 0.38 (5% EtOAc/hexanes). Spectral data matched those reported in the literature.[30]



3-21 **3-15**

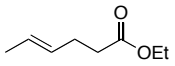
General Procedure to Form Carboxylic Acid 3-15 via Ester Hydrolysis:

To a solution of ester **3-21** (1.00 equiv) in THF (1.5 M) was added a solution of LiOH (5.00 equiv) in 1:1 H_2O:MeOH (3.6 M). The reaction mixture was heated to 60 °C for 1 h or until starting material was consumed by TLC analysis. The reaction mixture was then cooled to rt, partitioned between Et_2O (20 mL) and 1 M aq. NaOH (20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with 1 M aq. NaOH (3 x 10 mL). The aqueous washes were acidified to pH = 1 with 1 M aq. HCl and extracted with Et_2O (4 x 20 mL). Combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and the volatiles removed by atmospheric distillation. The crude products were carried on directly without further purification.



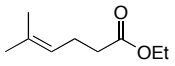
3-15c

4-Methylpent-4-enoic acid (3-15c). Ester **3-21**c (4.15 g, 29.3 mmol) was converted to **3-15**c following the general procedure for carboxylic acid formation to afford a clear oil (4.23 g, quant.): R_f = 0.50 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[31]



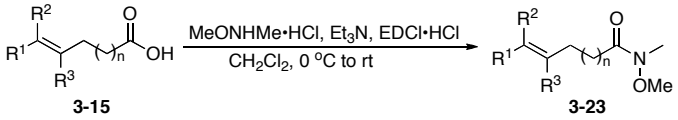
3-15d

(*E*)-Hex-4-enoic acid (3-15d). Ester **3-21**d (5.11 g, 35.9 mmol) was converted to **3-15**d following the general procedure for carboxylic acid formation to afford a clear oil (4.10 g, quant.): R_f = 0.48 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[32]



3-15e

5-Methylhex-4-enoic acid (3-15e). Ester **3-21**e (2.18 g, 14.0 mmol) was converted to **3-15**e following the general procedure for carboxylic acid formation to afford a clear oil (2.37 g, quant.): R_f = 0.47 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[33]

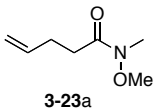


3-15 **3-23**

General Procedure to Form Amide 3-23 via Amide Coupling:

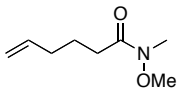
To a solution of carboxylic acid **3-15** (1.00 equiv) in CH_2Cl_2 (0.35 M) at 0 °C was added distilled Et_3N (3.00 equiv). A single portion of *N*,*O*-dimethylhydroxylamine hydrochloride (1.00 equiv) was added and the mixture was stirred for 10 min, followed by the addition of *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.00 equiv) in 2 equal portions

over 5 min. The resulting heterogeneous mixture was then slowly warmed to rt, stirred for 12 h, then quenched by the addition of H_2O (100 mL). The aqueous portion was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with 1 M aq. HCl (200 mL), sat. aq. $NaHCO_3$ (100 mL), and brine (50 mL). The organics were dried over anhydrous $MgSO_4$ and filtered. Solvent was removed by atmospheric distillation and amide **3-23** was purified by vacuum distillation.



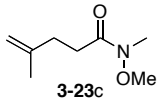
3-23a

***N*-Methoxy-*N*-methylpent-4-enamide (3-23a)**. 4-Pentenoic acid (**3-15**a, 3.67 mL, 35.7 mmol) was converted to **3-23**a following the general procedure for amide formation to afford a clear oil (2.15 g, 42%): bp 76 °C (15 torr); R_f=0.61 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[34]



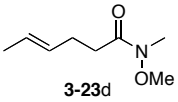
3-23b

***N*-Methoxy-*N*-methylhex-5-enamide (3-23b)**. 5-Hexenoic acid (**3-15**b, 5.00 g, 43.8 mmol) was converted to **3-23**b following the general procedure for amide formation to afford a clear oil (7.00 g, quant. not distilled, carried on directly): R_f = 0.60 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[35]



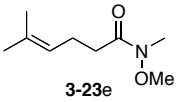
3-23c

***N*-Methoxy-*N*,4-dimethylpent-4-enamide (3-23c)**. Crude carboxylic acid **3-15**c (theoretically: 29.3 mmol) was converted to **3-23**c following the general procedure for amide formation to afford a clear oil (2.21 g, 48% over 2 steps): bp 82–85 °C (15 torr); R_f = 0.66 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[36]



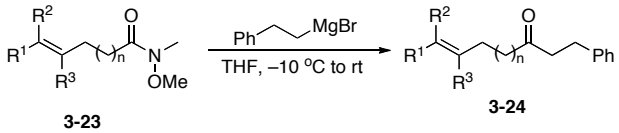
3-23d

(*E*)-*N*-Methoxy-*N*-methylhex-4-enamide (3-23d). Crude carboxylic acid **3-15**d (theoretically: 35.7 mmol) was converted to **3-23**d following the general procedure for amide formation to afford a clear oil (3.00 g, 53% over 2 steps): bp 88–91 °C (15 torr); R_f = 0.60 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[21]



3-23e

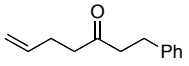
***N*-Methoxy-*N*,5-dimethylhex-4-enamide (3-23e)**. Crude carboxylic acid **3-15**e (theoretically: 14.0 mmol) was converted to **3-23**e following the general procedure for amide formation to afford a clear oil (0.85 g, 36% over 2 steps): bp 93–97 °C (15 torr); R_f = 0.59 (50% EtOAc/hexanes). Spectral data matched those reported in the literature.[37]



3-23 **3-24**

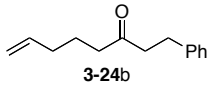
General Procedure to Form Ketone 3-24 via Grignard Addition:

A flame-dried Ar-flushed round bottom flask was charged with freshly ground Mg° turnings (12.3 mmol, 1.49 equiv) and THF (10 mL). A single crystal of I_2 was added, followed by dropwise addition of (2-bromoethyl)benzene (10.2 mmol, 1.25 equiv) while heating to reflux. The mixture was stirred for 30 min at reflux then cooled to rt. The resulting clear tan solution (1.25 equiv) was then added to a pre-cooled solution (–10 °C) of amide **3-23** (1.00 equiv) in THF (20 mL) dropwise over 10 min, then slowly warmed to rt. After 1 h, TLC indicated consumption of starting material. The resulting heterogeneous white slurry was partitioned between Et_2O (20 mL) and sat. aq. NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by column chromatography (0:100–10:90 EtOAc:hexanes) of the crude residue afforded **3-24**.



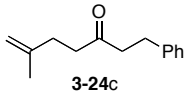
3-24a

1-Phenylhept-6-en-3-one (3-24a). Amide **3-23**a (1.18 g, 8.27 mmol) was converted to **3-24**a following the general procedure for ketone formation to afford a clear yellow oil (1.30 g, 85%): R_f = 0.49 (10% EtOAc/hexanes). Spectral data matched those reported in the literature.[38]



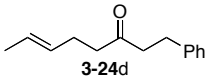
3-24b

1-Phenyloct-7-en-3-one (3-24b). Crude amide **3-23**b (theoretically: 43.8 mmol) was converted to **3-24**b following the general procedure for ketone formation to afford a clear yellow oil (5.02 g, 56% over 2 steps): R_f = 0.47 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.23 (m, 2H), 7.22–7.14 (m, 3H), 5.74 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.05–4.91 (m, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.03 (q, *J* = 7.1 Hz, 2H), 1.66 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1, 141.3, 138.1, 128.6, 128.4, 126.2, 115.3, 44.5, 42.2, 33.2, 29.9, 22.9; IR (thin film) 3063, 3027, 2932, 1714, 1453, 913, 699 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{18}ONa$ $[M + Na]^+$ 225.1255, found 225.1248.



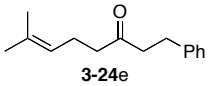
3-24c

6-Methyl-1-phenylhept-6-en-3-one (3-24c). Amide **3-23**c (1.30 g, 8.27 mmol) was converted to **3-24**c following the general procedure for ketone formation to afford a clear yellow oil (1.14 g, 68%): R_f = 0.50 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.27 (m, 2H), 7.21–7.18 (m, 3H), 4.73 (s, 1H), 4.64 (s, 1H), 2.93–2.90 (app. t, 2H), 2.77–2.74 (app. t, 2H), 2.56–2.52 (app. t, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5, 144.5, 141.2, 128.6, 128.4, 126.2, 110.3, 44.4, 41.3, 31.5, 29.8, 22.7; IR (thin film) 3064, 3026, 2931, 1714, 1452, 889 cm^{-1}. HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{18}ONa$ $[M + Na]^+$ 225.1255, found 225.1263.



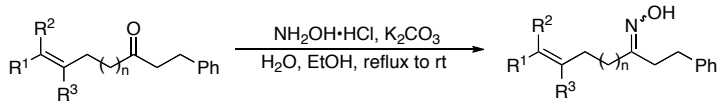
3-24d

(*E*)-1-Phenyloct-6-en-3-one (3-24d). Amide **3-23**d (1.30 g, 8.27 mmol) was converted to **3-24**d following the general procedure for ketone formation to afford a clear yellow oil (1.35 g, 81%): R_f = 0.49 (10% EtOAc/hexanes). Spectral data matched those reported in the literature.[Error! Bookmark not defined.]



3-24e

7-Methyl-1-phenyloct-6-en-3-one (3-24e). Amide **3-23**d (850. mg, 4.96 mmol) was converted to **3-24**e following the general procedure for ketone formation to afford a clear yellow oil (440 mg, 41%): R_f = 0.48 (10% EtOAc/hexanes). Spectral data matched those reported in the literature.[37]

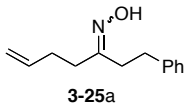


3-24 **3-25**

General Procedure to Form Oxime 3-25 via Condensation:

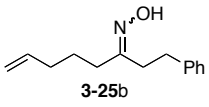
To a solution of hydroxylamine hydrochloride (1.25 equiv) in H_2O (1.33 M) was added K_2CO_3 (1.25 equiv) slowly in small portions, followed by a solution of ketone **3-24** (1.00 equiv) in EtOH (1.00 M). The resulting cloudy mixture was brought to reflux for 4 h and cooled to rt. Additional hydroxylamine hydrochloride and K_2CO_3 (1.00 equiv each) were added and the reaction mixture was refluxed for 1 h at which time TLC indicated consumption of starting material. The reaction mixture was cooled to rt and partitioned between Et_2O (20 mL) and H_2O (20 mL). The aqueous portion was extracted with Et_2O (20 mL) and the combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

Purification by column chromatography (0:1 – 1:5 EtOAc:hexanes) of crude residue afforded **3-25**. Products were isolated as a 1:1 mixture of *E:Z* oximes.



3-25a

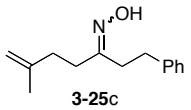
1-Phenylhept-6-en-3-one oxime (3-25a). Ketone **3-24**a (1.27 g, 6.75 mmol) was converted to **3-25**a following the general procedure for oxime formation to afford a clear yellow oil (1.55 g, quant.): R_f = 0.30 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (br. s, 2H), 7.30–7.25 (m, 4H), 7.25–7.17 (m, 6H), 5.89–5.74 (m, 2H), 5.12–4.94 (m, 4H), 2.89–2.81 (app. q, 4H), 2.66–2.63 (app t, 2H), 2.53–2.45 (m, 4H), 2.34–2.19 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 160.5, 141.5, 141.4, 137.6, 137.5, 128.59, 128.57, 128.4 (2), 126.3, 126.2, 115.4, 115.3, 36.3, 34.1, 32.7, 31.7, 30.3, 30.2, 29.7, 27.5; IR (thin film) 3241, 3082, 2927, 1641, 1496, 1453, 915 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{13}H_{17}NONa$ $[M + Na]^+$ 226.1208, found 226.1200.



3-25b

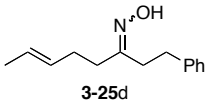
1-Phenyloct-7-en-3-one oxime (3-25b). Ketone **3-24**b (5.00 g, 24.7 mmol) was converted to **3-25**b following the general procedure for oxime formation to afford a clear yellow oil (5.40 g, quant.): R_f = 0.24 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (br. s, 2H), 7.28 (t, *J* = 7.6 Hz, 4H), 7.25–7.14 (m, 6H), 5.88–5.71 (m, 2H), 5.08–4.94 (m, 4H), 2.91–2.80 (m, 4H), 2.68–2.61 (m, 2H), 2.55–2.47 (m, 2H), 2.43–2.35 (m, 2H), 2.18–2.01 (m, 6H), 1.68–1.56 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 161.0, 141.6, 141.4, 138.20, 138.18, 128.59, 128.57, 128.4 (2), 126.3 (2), 115.2 (2), 36.2, 34.1, 34.0, 33.4, 32.7, 31.8, 30.1, 27.6, 25.4, 25.0; IR (thin

film) 3244, 3078, 2928, 1640, 1496, 1454 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{20}NO$ $[M + H]^+$ 218.1545, found 218.1545.



3-25c

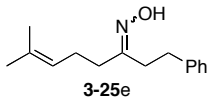
6-Methyl-1-phenylhept-6-en-3-one oxime (3-25c). Ketone **3-24**c (1.30 g, 6.40 mmol) was converted to **3-25**c following the general procedure for oxime formation to afford a clear yellow oil (1.48 g, quant.): R_f = 0.27 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (br. s, 2H), 7.34–7.25 (m, 4H), 7.25–7.13 (m, 6H), 4.79–4.65 (m, 4H), 2.89–2.83 (app. q, 4H), 2.67–2.63 (app. t, 2H), 2.55–2.49 (app. q, 4H), 2.30–2.15 (m, 6H), 1.76 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.84, 160.82, 145.0, 144.8, 141.5, 141.4, 128.60, 128.58, 128.4 (2), 126.3, 126.2, 110.6, 110.5, 36.2, 34.2, 33.4, 33.0, 32.7, 31.8, 30.1, 26.5, 22.54, 22.50; IR (thin film) 3239, 3083, 2931, 1650, 1496, 1453, 890 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{19}NONa$ $[M + Na]^+$ 240.1364, found 240.1355.



3-25d

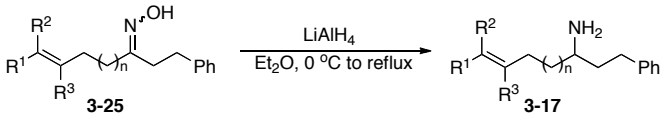
(6*E*)-1-Phenyloct-6-en-3-one oxime (3-25d). Ketone **3-24**d (1.30 g, 6.40 mmol) was converted to **3-25**d following the general procedure for oxime formation to afford a clear yellow oil (1.24 g, 89%): R_f = 0.25 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (br. s, 2H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.26–7.16 (m, 6H), 5.57–5.35 (m, 4H), 2.89–2.80 (app. q, 4H), 2.66–2.60 (app. t, 2H), 2.53–2.47 (app. t, 2H), 2.46–2.40 (app. t, 2H), 2.26–2.20 (app. q, 2H), 2.18 (s, 4H), 1.64 (t, *J* = 5.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 160.8, 141.6, 141.5, 130.2, 130.0, 128.59, 128.57, 128.4 (2), 126.24, 126.21, 126.0, 125.9, 36.4, 34.7, 32.6, 31.7, 30.1, 29.3, 28.6, 28.3,

18.06, 18.04; IR (thin film) 3241, 3026, 2918, 1496, 1452, 965 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{19}NONa$ $[M + Na]^+$ 240.1364, found 240.1373.



3-25e

7-Methyl-1-phenyloct-6-en-3-one oxime (3-25e). Ketone **3-24e** (372 mg, 1.72 mmol) was converted to **3-25e** following the general procedure for oxime formation to afford a clear yellow oil (400 mg, 99%): R_f = 0.23 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (br. s, 2H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.25–7.15 (m, 6H), 5.14 (t, *J* = 7.1 Hz, 1H), 5.08 (t, *J* = 6.4 Hz, 1H), 2.89–2.82 (app. q, 4H), 2.67–2.61 (app. t, 2H), 2.54–2.47 (app. t, 2H), 2.43–2.36 (app. t, 2H), 2.27–2.12 (m, 6H), 1.69 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 161.1, 141.6, 141.5, 132.9, 132.7, 128.59, 128.58, 128.4 (2), 126.24, 126.21, 123.4, 123.2, 36.5, 34.8, 32.7, 31.8, 30.1, 28.2, 25.8 (2), 24.9, 24.3, 17.9, 17.8; IR (thin film) 3234, 2925, 1496, 1453, 960, 699 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{15}H_{21}NONa$ $[M + Na]^+$ 254.1521, found 254.1509.

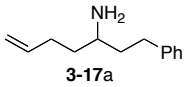


3-25 **3-17**

General Procedure to Form Amine 3-17 via Oxime Reduction:

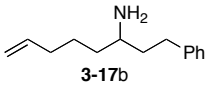
To a stirring suspension of $LiAlH_4$ (2.00 equiv) in Et_2O (0.5 M) at 0 °C was added a solution of oxime **3-25** (1.00 equiv) in Et_2O (0.5 M) at an approximate rate of 1 mL/min (gas evolution was observed). The heterogeneous grey reaction mixture was warmed to rt, then heated to reflux for 16 h, or until TLC analysis of a quenched aliquot indicated consumption of starting material. The reaction mixture was cooled to rt and treated sequentially with H_2O (1 mL/g of $LiAlH_4$), 10%

w/w aq. NaOH (1 mL/g of $LiAlH_4$) and H_2O (3 mL/g of $LiAlH_4$) at a rate sufficient to prevent reflux, then stirred vigorously for 1 h. The resulting white heterogeneous mixture was filtered through a pad of Celite, washed with Et_2O (3 x 20 mL), and concentrated *in vacuo* to give a light yellow oil. Purification by column chromatography with Et_3N-deactivated SiO_2 (0:1:99 – 99:1:0 EtOAc:Et_3N:hexanes) of the crude residue afforded **3-17**.



3-17a

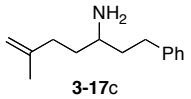
1-Phenylhept-6-en-3-amine (3-17a). Oxime **3-25**a (1.55 g, 6.76 mmol) was converted to **3-17**a following the general procedure for amine formation to afford a clear oil (1.17 g, 92%): R_f = 0.12 (49:1:50 EtOAc:Et_3N:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 13.7, 6.0 Hz, 2H), 7.30–7.20 (m, 3H), 5.88 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.09 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 2.87–2.77 (m, 2H), 2.75–2.65 (m, 1H), 2.24 (td, *J* = 15.0, 6.4 Hz, 1H), 2.15 (td, *J* = 15.0, 7.0 Hz, 1H), 1.87–1.78 (m, 1H), 1.64 (tdd, *J* = 14.4, 8.8, 6.0 Hz, 2H), 1.51–1.41 (m, 1H), 1.28 (br. s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 138.7, 128.49, 128.46, 125.9, 114.7, 50.5, 40.0, 37.4, 32.7, 30.6; IR (thin film) 3372, 3026, 2924, 1639, 1453, 910 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{13}H_{20}N$ $[M + H]^+$ 190.1596, found 190.1587.



3-17b

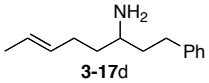
1-Phenyloct-7-en-3-amine (3-17b). Oxime **3-25**b (5.40 g, 24.7 mmol) was converted to **3-17**b following the general procedure for amine formation to afford a clear oil (4.55 g, 90%): R_f = 0.10 (49:1:50 EtOAc:Et_3N:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 13.3, 5.3 Hz, 2H), 7.18 (dd, *J* = 12.0, 7.6 Hz, 3H), 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.5 Hz,

1H), 4.95 (d, *J* = 10.2 Hz, 1H), 2.79–2.69 (m, 2H), 2.67–2.57 (m, 1H), 2.13–1.99 (m, 2H), 1.80–1.69 (m, 1H), 1.62–1.53 (m, 1H), 1.52–1.36 (m, 3H), 1.35–1.17 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 138.8, 128.43, 128.41, 125.8, 114.6, 50.8, 40.0, 37.7, 33.9, 32.7, 25.5; IR (thin film) 3429, 3365, 3287, 3063, 3026, 2999, 2975, 2929, 2857, 1640, 1579, 1455, 910 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{22}N$ $[M + H]^+$ 204.1752, found 204.1743.



3-17c

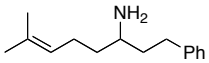
6-Methyl-1-phenylhept-6-en-3-amine (3-17c). Oxime **3-25**c (1.48 g, 5.44 mmol) was converted to **3-17**c following the general procedure for amine formation to afford a clear oil (1.09 g, 98%): R_f = 0.10 (49:1:50 EtOAc:Et_3N:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2H), 7.22–7.16 (m, 3H), 4.71 (br. s, 1H), 4.69 (br. s, 1H), 2.80–2.71 (m, 2H), 2.68–2.59 (m, 1H), 2.17–2.08 (m, 1H), 2.08–1.99 (m, 1H), 1.81–1.74 (m, 1H), 1.73 (s, 3H), 1.66–1.54 (m, 2H), 1.48–1.38 (m, 1H), 1.29 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 142.5, 128.6, 128.5, 125.9, 110.0, 50.8, 40.0, 36.2, 34.5, 32.8, 22.6; IR (thin film) 3372, 3026, 2931, 1648, 1453, 886 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{22}N$ $[M + H]^+$ 204.1752, found 204.1747.



3-17d

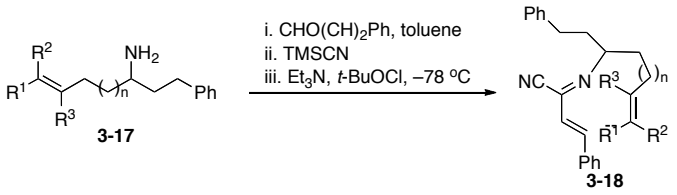
(*E*)-1-Phenyloct-6-en-3-amine (3-17d). Oxime **3-25**d (1.21 g, 5.56 mmol) was converted to **3-17**d following the general procedure for amine formation to afford a clear oil (1.06 g, 94%): R_f = 0.11 (49:1:50 EtOAc:Et_3N:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (m, 2H), 7.22–7.11 (m, 3H), 5.51–5.34 (m, 2H), 2.79–2.68 (m, 2H), 2.66–2.57 (m, 1H), 2.13–2.04 (m, 1H), 2.04–1.94 (m, 1H), 1.79–1.69 (m, 1H), 1.64 (d, *J* = 4.7 Hz, 3H), 1.61–1.47 (m, 2H),

1.39–1.32 (m, 1H), 1.30 (br. s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 131.1, 128.4 (2), 125.8, 125.1, 50.4, 39.9, 38.0, 32.6, 29.3, 18.0; IR (thin film) 3364, 3025, 2918, 1582, 1453, 967 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{14}H_{22}N$ $[M + H]^+$ 204.1752, found 204.1749.



3-17e

7-Methyl-1-phenyloct-6-en-3-amine (3-17e). Oxime **3-25**e (396 mg, 1.76 mmol) was converted to **3-17**e following the general procedure for amine formation to afford a clear oil (290 mg, 76%): R_f = 0.09 (49:1:50 EtOAc:Et_3N:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.25 (m, 2H), 7.22–7.15 (m, 3H), 5.11 (dddd, *J* = 8.5, 7.1, 2.6, 1.3 Hz, 1H), 2.79–2.70 (m, 2H), 2.62 (ddd, *J* = 13.7, 10.4, 6.0 Hz, 1H), 2.15–1.96 (m, 2H), 1.75 (dddd, *J* = 13.6, 10.7, 6.0, 4.8 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.60–1.55 (m, 1H), 1.54–1.46 (m, 1H), 1.33 (dddd, *J* = 13.7, 9.2, 7.9, 6.0 Hz, 1H), 1.19 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 131.8, 128.5 (2), 125.9, 124.4, 50.7, 40.1, 38.3, 32.8, 25.9, 24.8, 17.8; IR (thin film) 3374, 3026, 2916, 1603, 1453, 699 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{15}H_{24}N$ $[M + H]^+$ 218.1909, found 218.1917.

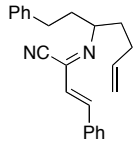


3-17 **3-18**

General Procedure to Form Cyano Enamine 3-18 via an Oxidative Strecker Reaction:

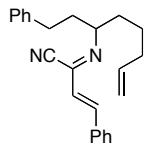
A mixture of amine **3-17** (1.00 equiv) and *trans*-cinnamaldehyde (1.00 equiv) in toluene (0.75 M) was stirred for 40 min at room temperature. The solution was treated with TMSCN (1.00 equiv) and stirred for 2 h. The mixture was cooled to –78 °C and Et_3N (1.10 equiv) was added. A solution of *t*-butyl hypochlorite (0.6 M in toluene) was added dropwise until TLC

analysis indicated consumption of imine intermediate. The reaction was quenched with sat. aq. $Na_2S_2O_3$. The mixture was extracted with EtOAc (4 x 10 mL). The organic layers were combined, washed with sat. aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, and filtered. The resulting solution was concentrated *in vacuo*. Purification of the crude residue by column chromatography with Et_3N-deactivated SiO_2 (5:1:94 EtOAc:Et_3N:hexanes) afforded **3-18**.



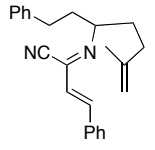
3-18a

(*Z*)-*N*-(1-Phenylhept-6-en-3-yl)cinnamimidoyl cyanide (3-18a). Amine **3-17**a (50. mg, 0.26 mmol) was converted to **3-18**a following the general procedure for cyano enamine formation to afford a clear yellow oil (73 mg, 86%): R_f = 0.32 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 16.4 Hz, 1H), 7.20–7.16 (m, 2H) 7.10–7.04 (m, 3H), 7.03–6.94 (m, 5H), 6.91 (d, *J* = 16.5 Hz, 1H), 5.73 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.07–4.96 (m, 2H), 3.94 (dt, *J* = 8.5, 4.7 Hz, 1H), 2.51 (t, *J* = 8.3 Hz, 2H), 2.01–1.89 (m, 3H), 1.81 (ddq, *J* = 8.9, 3.9, 2.8 Hz, 1H), 1.76–1.68 (m, 1H), 1.63–1.54 (m, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 142.3, 141.90, 141.89, 138.0, 134.9, 130.1, 129.0, 128.8, 128.7, 128.4, 126.4, 126.3, 115.3, 110.0, 68.5, 38.4, 35.8, 33.1, 30.9; IR (thin film) 3027, 2941, 2220, 1628, 1583, 1450, 967 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{23}H_{24}N_2Na$ $[M + Na]^+$ 351.1837, found 351.1835.



3-18b

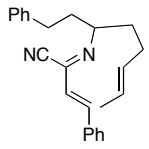
(*Z*)-*N*-(1-Phenyloct-7-en-3-yl)cinnamimidoyl cyanide (3-18b). Amine **3-17**b (123 mg, 0.60 mmol) was converted to **3-18**b following the general procedure for cyano enamine formation to afford a clear yellow oil (164 mg, 80%): R_f = 0.33 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 16.3 Hz, 1H), 7.19–7.16 (m, 2H), 7.11–7.05 (m, 3H), 7.02–6.94 (m, 5H), 6.92 (d, *J* = 16.5 Hz, 1H), 5.71 (ddt, *J* = 14.0, 10.1, 6.8 Hz, 1H), 5.09–5.00 (m, 1H), 4.97 (d, *J* = 10.1 Hz, 1H), 3.98–3.84 (m, 1H), 2.52 (m, 2H), 1.95 (app. heptet, 3H), 1.88–1.79 (m, 1H), 1.64–1.57 (m, 1H), 1.55–1.45 (m, 1H), 1.35–1.27 (m, 2H); ^{13}C NMR (126 MHz, C_6D_6) δ 142.2, 142.0, 141.6, 138.6, 134.9, 130.0, 129.0, 128.78, 128.76, 128.4, 126.4, 126.3, 115.1, 110.0, 69.0, 38.5, 36.1, 34.0, 33.2, 25.9; IR (thin film) 3027, 2938, 2220, 1629, 1583, 1450, 967 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{24}H_{26}N_2Na$ [M + Na]$^+$ 365.1994, found 365.1989.



3-18c

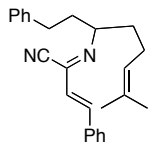
(*Z*)-*N*-(6-Methyl-1-phenylhept-6-en-3-yl)cinnamimidoyl cyanide (3-18c). Amine **3-17**c (50. mg, 0.25 mmol) was converted to **3-18**c following the general procedure for cyano enamine formation to afford a clear oil (64 mg, 75%): R_f = 0.30 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.42 (d, *J* = 16.4 Hz, 1H), 7.20–7.16 (m, 2H), 7.11–7.04 (m, 3H), 7.03–6.94 (m, 5H), 6.93–6.88 (d, *J* = 16.5 Hz, 1H), 4.80 (d, *J* = 9.1 Hz, 2H), 3.95 (tt, *J* = 8.5, 3.3 Hz, 1H), 2.53 (t, *J* = 8.3 Hz, 2H), 1.97 (td, *J* = 8.3, 4.4 Hz, 3H), 1.83 (ddd, *J* = 16.0, 10.4, 5.3 Hz, 2H),

1.72 (dq, J = 6.7, 3.2 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 145.0, 142.3, 141.91, 141.88, 134.9, 130.1, 129.0, 128.78, 128.76, 128.4, 126.4, 126.3, 110.8, 110.0, 68.8, 38.5, 34.7, 34.6, 33.2, 22.6; IR (thin film) 3027, 2941, 2220, 1628, 1583, 1450, 967 cm^{-1}; HRMS (ESI/MeOH) m / z calcd for $C_{24}H_{26}N_2Na$ [M + Na]$^+$ 365.1994, found 365.1993.



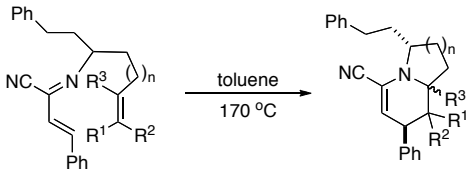
3-18d

(*Z*)-*N*-((*E*)-1-Phenyloct-6-en-3-yl)cinnamimidoyl cyanide (3-18d). Amine **3-17**d (100. mg, 0.50 mmol) was converted to **3-18**d following the general procedure for cyano enamine formation to afford a clear yellow oil (127 mg, 74%): R_f = 0.32 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.42 (d, J = 16.4 Hz, 1H), 7.19–7.16 (m, 2H), 7.11–7.05 (m, 3H), 7.04–6.95 (m, 5H), 6.92 (d, J = 16.5 Hz, 1H), 5.46–5.35 (m, 2H), 3.98 (dt, J = 8.6, 4.5 Hz, 1H), 2.52 (t, J = 8.4 Hz, 2H), 2.03–1.91 (m, 3H), 1.84 (ddt, J = 13.3, 9.2, 4.1 Hz, 1H), 1.75 (dq, J = 15.2, 7.7 Hz, 1H), 1.63 (d, J = 4.6 Hz, 3H), 1.63–1.57 (m, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 142.1, 142.0, 141.9, 135.0, 130.6, 130.0, 129.0, 128.77, 128.76 (2), 126.5, 126.3, 126.0, 110.0, 68.5, 38.6, 36.4, 33.2, 29.8, 18.2; IR (thin film) 3027, 2918, 2220, 1629, 1583, 1450, 966 cm^{-1}; HRMS (ESI/MeOH) m / z calcd for $C_{24}H_{26}N_2Na$ [M + Na]$^+$ 365.1994, found 365.1990.



3-18e

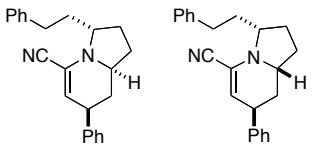
(*Z*)-*N*-(7-Methyl-1-phenyloct-6-en-3-yl)cinnamimidoyl cyanide (3-18e). Amine **3-17**e (50. mg, 0.23 mmol) was converted to **3-18**e following the general procedure for cyano enamine formation to afford a clear yellow oil (55 mg, 67%): R_f = 0.31 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.42 (d, *J* = 16.4 Hz, 1H), 7.20–7.14 (m, 2H) 7.10–7.04 (m, 3H), 7.03–6.92 (m, 6H), 5.18 (t, *J* = 7.3 Hz, 1H), 4.01 (tt, *J* = 8.4, 4.0 Hz, 1H), 2.54 (t, *J* = 8.3 Hz, 2H), 2.08–1.94 (m, 3H), 1.87 (dtd, *J* = 12.9, 8.2, 3.7 Hz, 1H), 1.82–1.73 (m, 1H), 1.71 (s, 3H), 1.65 (tq, *J* = 8.8, 4.2 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 142.1, 142.0, 141.9, 135.0, 132.2, 130.0, 129.0, 128.77, 128.76, 128.4, 126.5, 126.3, 124.2, 110.0, 68.7, 38.6, 36.6, 33.2, 25.9, 25.3, 17.9; IR (thin film) 3025, 2928, 2219, 1628, 1582, 1450, 967 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{25}H_{28}N_2Na$ [M + Na]$^+$ 379.2150, found 379.2143.



3-18 **3-19**

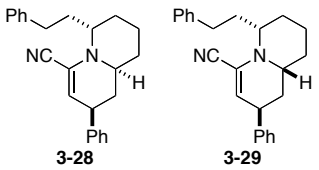
General Procedure for the Intramolecular Diels–Alder Reaction:

An acid/base treated microwave vial was charged with a solution of cyano enamine **3-18** in wet toluene (0.04 M), sealed and heated thermally to 170 °C for 24 hours. The reaction was cooled to rt, concentrated *in vacuo*, and purified by column chromatography (5:1:94 – 10:1:89 EtOAc:Et_3N:hexanes).



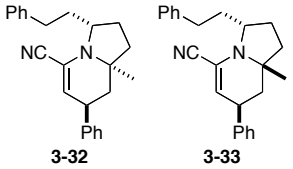
3-30 **3-31**

3-Phenethyl-7-phenyl-1,2,3,7,8,8a-hexahydroindolizine-5-carbonitrile (**3-30** and **3-31**). Cyano enamine **3-18**a (20. mg, 0.06 mmol) was converted to indolizidine **3-30** and **3-31** following the general procedure for the Diels–Alder reaction to afford a clear yellow oil (13.0 mg, 65%) as a 2:1 mixture of **3-30** and **3-31**, respectively. A small amount of indolizidine **3-30** and **3-31** was separated for characterization, but most of it was recovered as a mixture of the two diastereomers. Indolizidine **3-30**: R_f = 0.56 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.15 (m, 10H), 5.31 (br. s, 1H), 3.70–3.62 (m, 2H), 3.57–3.53 (m, 1H). 2.74–2.64 (m, 2H), 2.23–2.16 (m, 2H), 2.13–2.03 (m, 2H), 1.83–1.75 (m, 1H), 1.72–1.67 (m, 1H), 1.62–1.56 (m, 1H), 1.31 (q, *J* = 12 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 141.8, 128.8, 128.6, 128.5, 127.2, 126.9, 126.0, 119.8, 116.8, 116.2, 61.8, 57.3, 40.8, 38.0, 36.6, 32.6, 31.0, 29.4; IR (thin film) 3060, 3026, 2942, 2860, 2223, 1600 cm^{-1}, HRMS (ESI/MeOH) *m* / *z* calcd for $C_{23}H_{24}N_2Na$ $[M + Na]^+$ 351.1837, found 351.1830. Indolizidine **3-31**: R_f = 0.58 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 4H), 7.23–7.19 (m, 4H), 7.17–7.16 (m, 2H), 5.43 (d, *J* = 5.2 Hz, 1H), 3.81 (t, *J* = 7.7 Hz, 1H), 3.61 (t, *J* = 5.5 Hz, 1H), 3.14–3.09 (m, 1H), 2.71–2.59 (m, 2H), 2.08–1.90 (m, 4H), 1.82–1.78 (m, 1H), 1.62–1.46 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 141.7, 128.6, 128.5 (2), 128.4, 126.6, 126.1, 118.7, 116.3, 113.0, 60.2, 52.3, 39.1, 37.5, 37.1, 33.5, 30.1, 28.4; IR (thin film) 3061, 3026, 2926, 2859, 2225, 1668, 1453 cm^{-1}, HRMS (ESI/MeOH) *m* / *z* calcd for $C_{23}H_{24}N_2Na$ $[M + Na]^+$ 351.1837, found 351.1848.



3-28 **3-29**

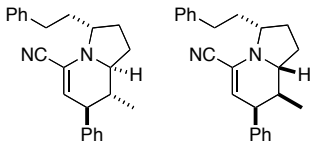
6-Phenethyl-2-phenyl-2,6,7,8,9,9a-hexahydro-1*H*-quinolizine-4-carbonitrile (**3-28** and **3-29**). Cyano enamine **3-18**b (100. mg, 0.29 mmol) was converted to quinolizidine **3-28** and **3-29** following the general procedure for the Diels–Alder reaction to afford a clear yellow oil (51 mg, 51%) as an inseparable mixture of **3-28** and **3-29** (1:2 ratio): R_f = 0.59 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 6H), 7.24–7.15 (m, 10H), 5.48 (d, *J* = 4.0Hz, 1H), 5.40–5.39 (m, 0.6H), 3.86–3.82 (m, 0.6H), 3.56 (app. q, 1.6H), 3.44–3.38 (m, 1H), 3.16 (t, *J* = 11.3 Hz, 0.6H), 3.09–3.04 (m, 1H), 2.78–2.62 (m, 3.2H), 2.28–2.20 (m, 1H), 2.08–2.01 (m, 1.2H), 1.95–1.73 (m, 6H), 1.72–1.61 (m, 5H), 1.59–1.50 (m, 2.2H), 1.29–1.21 (m, 0.6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4, 144.3, 142.0, 141.9, 128.8, 128.65, 128.61, 128.59, 128.5, 128.4, 128.0, 127.2, 126.9, 126.7, 126.1, 126.0, 122.8, 121.4, 118.8, 117.7, 117.2, 116.2, 59.1, 56.4, 52.2, 51.2, 40.2, 39.9, 37.9, 37.8, 37.7, 33.5, 33.4, 32.5, 30.6, 27.3, 27.1, 27.0, 19.6, 18.7; IR (thin film) 3025, 2937, 2222, 1603, 1453, 700 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{24}H_{26}N_2Na$ $[M + Na]^+$ 365.1994, found 365.1984.



3-32 **3-33**

8a-Methyl-3-phenethyl-7-phenyl-1,2,3,7,8,8a-hexahydroindolizine-5-carbonitrile (**3-32** and **3-33**). Cyano enamine **3-18**c (20. mg, 0.06 mmol) was converted to indolizidine **3-32** and **3-33** following the general procedure for the Diels–Alder reaction to afford a clear yellow oil (15.0 mg, 75%) as an inseparable mixture of **3-32** and **3-33** (2:1 ratio): R_f = 0.61 (10%

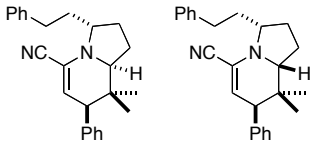
EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 7H), 7.25–7.17 (m, 8H), 5.69 (d, *J* = 4.7 Hz, 0.5H), 5.36 (br. s, 1H), 3.86–3.82 (m, 0.5H), 3.70–3.68 (app. t, 0.5H), 3.63 (septet, *J* = 4.0 Hz, 1H), 3.48 (ddd, *J* = 11.9, 5.9, 2.0 Hz, 1H), 2.73–2.59 (m, 3H), 2.42 (d, *J* = 13.4 Hz, 0.5H), 2.28–2.24 (m, 1H), 2.09–1.93 (m, 3H), 1.86–1.68 (m, 6H), 1.58–1.50 (m, 0.5H), 1.28 (t, *J* = 12.4 Hz, 1H), 1.23 (s, 3H), 0.62 (s, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 143.8, 141.9, 141.6, 128.8, 128.6, 128.52 (2), 128.46, 128.4, 127.6, 127.4, 126.9, 126.12, 126.07, 126.0, 119.6, 117.8, 117.3, 116.6, 116.0, 114.0, 63.0, 60.9, 60.8, 59.3, 43.2, 41.5, 39.11, 39.07, 39.0, 38.2, 37.4, 36.8, 33.5, 32.8, 28.8, 27.0, 26.2, 25.2; IR (thin film) 3025, 2927, 2222, 1601, 1453, 698 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{24}H_{26}N_2Na$ $[M + Na]^+$ 365.1994, found 365.1989.



3-34 **3-35**

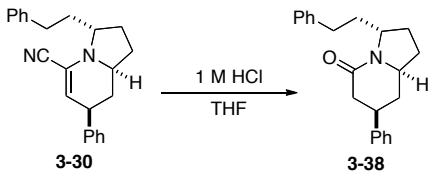
8-Methyl-3-phenethyl-7-phenyl-1,2,3,7,8,8a-hexahydroindolizine-5-carbonitrile (**3-34** and **3-35**). Cyano enamine **3-18**d (20. mg, 0.06 mmol) was converted to indolizidine **3-34** and **3-35** following the general procedure for the Diels–Alder reaction to afford a clear yellow oil (15.0 mg, 75%) as an inseparable mixture of **3-34** and **3-35** (1:4 ratio): R_f = 0.60 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.15 (m, 10H), 7.11 (d, *J* = 7.1 Hz, 0.5H), 7.08 (d, *J* = 7.2 Hz, 2H), 5.39 (d, *J* = 6.0 Hz, 1H), 5.17 (d, *J* = 2.4 Hz, 0.25H), 3.86–3.83 (m, 1H), 3.74–3.69 (m, 0.25H), 3.38 (t, *J* = 5.5 Hz, 1H), 3.22–3.17 (m, 0.25H), 3.08–3.00 (m, 1.25H), 2.71–2.58 (m, 2.5H), 2.31–2.24 (m, 0.25H), 2.18–2.11 (m, 0.5H), 2.10–2.03 (m, 1H), 1.99–1.90 (m, 2H), 1.84–1.79 (m, 1.25H), 1.70–1.50 (m, 3.5H), 1.32–1.25 (m, 0.25H), 0.78 (d, *J* = 6.5 Hz, 0.75H), 0.63 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 141.74,

141.68, 141.3, 130.1, 128.60, 128.56, 128.505, 128.500, 128.46, 128.3, 127.9, 126.9, 126.8, 126.04, 125.96, 118.4, 117.6, 116.6, 116.4, 115.9, 114.4, 63.2, 61.2, 60.4, 57.7, 48.0, 45.1, 38.4, 37.9, 37.7, 37.1, 33.5, 32.3, 30.2, 29.8, 29.3, 28.4, 16.6, 14.6; IR (thin film) 3025, 2962, 2224, 1603, 1453, 700 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{24}H_{26}N_2Na$ $[M + Na]^+$ 365.1994, found 365.1997.



3-36 **3-37**

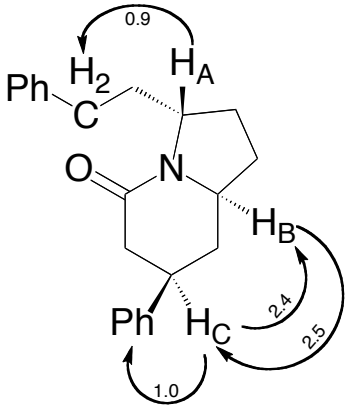
8,8-Dimethyl-3-phenethyl-7-phenyl-1,2,3,7,8,8a-hexahydroindolizidine-5-carbonitrile (**3-36** and **3-37**). Cyano enamine **3-18**e (20. mg, 0.06 mmol) was converted to indolizidine **3-36** and **3-37** following the general procedure for the Diels–Alder reaction to afford a clear yellow oil (13.4 mg, 67%) as an inseparable mixture of **3-36** and **3-37** (1:2 ratio): R_f = 0.61 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.18 (m, 12.8H), 7.16–7.11 (m, 3.2H), 5.19 (d, *J* = 5.4 Hz, 1H), 5.17 (d, *J* = 2.1 Hz, 0.6H), 3.86–3.78 (m, 1.6H), 3.44–3.41 (m, 1.2H), 3.17 (t, *J* = 8.2 Hz, 1H), 3.06 (d, *J* = 5.4 Hz, 1H), 2.74–2.62 (m, 3.2H), 2.18–1.95 (m, 4H), 1.83–1.76 (m, 2H), 1.73–1.68 (m, 0.6H), 1.66–1.56 (m, 3H), 0.89 (s, 3H), 0.82 (s, 1.8H), 0.54 (s, 3H), 0.53 (s, 1.8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 141.8, 141.7, 140.7, 130.2, 130.0, 128.58, 128.55 (2), 128.5, 127.82, 127.77, 126.9, 126.8, 126.04. 126.02, 118.1, 116.8, 116.3, 116.1, 114.1, 111.1, 65.9, 60.93, 60.88, 59.8, 52.6, 52.0, 38.9, 37.1, 34.0, 33.3, 32.6, 31.5, 29.5, 28.8, 25.4, 25.1, 24.4, 24.0, 23.0, 15.0; IR (thin film) 3026, 2964, 2224, 1602, 1424, 701 cm^{-1}; HRMS (ESI/MeOH) *m* / *z* calcd for $C_{25}H_{28}N_2Na$ $[M + Na]^+$ 379.2150, found 379.2147.



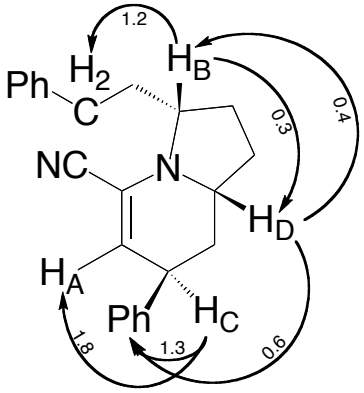
3-Phenethyl-7-phenylhexahydroindolizin-5(1*H*)-one (**3-38**). Indolizidine **3-30** was hydrolyzed to corresponding amide **3-38** in order to determine the relative configuration of **3-30**. A solution of indolizidine **3-30** (10 mg, 0.03 mmol) in 1 M HCl (1.5 mL, 0.02 M) and THF (1.5 mL, 0.02M) was stirred overnight at room temperature. The mixture was quenched with sat. aq $NaHCO_3$, The mixture was extracted with CH_2Cl_2 (4 x 1 mL). The organic layers were combined, washed with sat. aq. NaCl, dried over anhydrous $MgSO_4$, and filtered. The resulting solution was concentrated *in vacuo*. Purification by preparative TLC plate (20:80 EtOAc: CH_2Cl_2) resulted in indolizidinone **3-38**, the yield was not recorded. R_f = 0.62 (20% EtOAc/ CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, 2H), 7.29–7.23 (m, 5H), 7.20–7.16 (m, 3H), 4.23–4.19 (m, 1H), 3.61 (app. heptet, 1H), 3.01 (app. tdd, 1H), 2.73–2.64 (m, 3H), 2.46–2.34 (m, 2H), 2.29–2.25 (m, 1H), 2.19 (app. dt, 1H), 2.12 (quintet, J = 6.0 Hz, 1H), 1.78–1.70 (m, 1H), 1.64–1.58 (m, 1H), 1.53 (q, J = 1.53 Hz, 1H), 1.48–1.41 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 144.0, 141.9, 128.9, 128.5, 128.4, 126.9, 126.6, 125.9, 58.8, 56.9, 40.0, 39.2, 36.8, 35.9, 33.2, 31.9, 29.2; IR (thin film) 3026, 2923, 2860, 1635, 1453 cm^{-1}; HRMS (ESI/MeOH) m/z calcd for $C_{22}H_{25}NONa$ $[M + Na]^+$ 342/1834, found 342.1830.

NOE Correlation

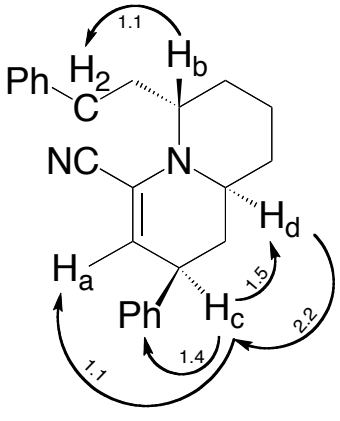
Numbers reported by the arrows are calculated NOE enhancement values. Values under 0.5 are not shown unless significant (Compound **3-31**). No correlations to or from aliphatic protons are labeled. Protons labels are consistent with labels shown on the ^{1}H NMR and NOE spectra in the appendix (beginning downfield with H_A and moving to the right). For compounds where the major and minor diastereomer were inseparable, capital letters are used to label the major diastereomer (H_A, H_B, etc.) and lower case letters are used to label the minor diastereomer (H_a, H_b, etc.). Proton signals that drastically overlapped on the ^{1}H NMR spectrum within the same molecule receive the same label (compound **3-37**, H_c).



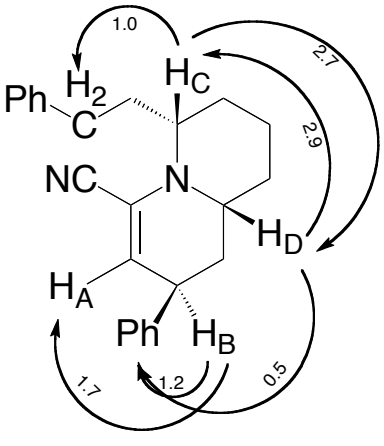
Compound **3-38**



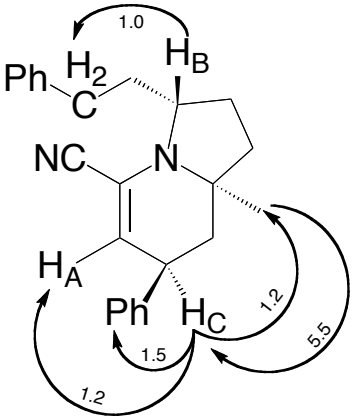
Compound **3-31**



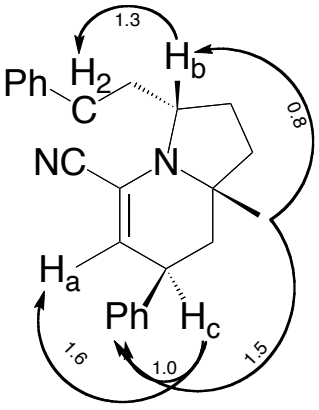
Compound **3-28**



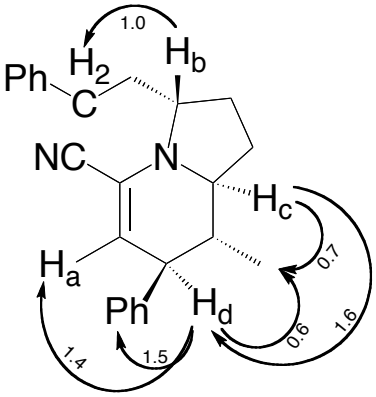
Compound **3-29**



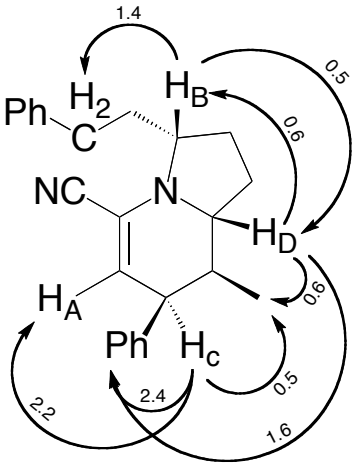
Compound **3-32**



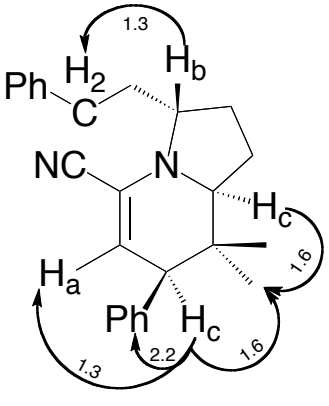
Compound **3-33**



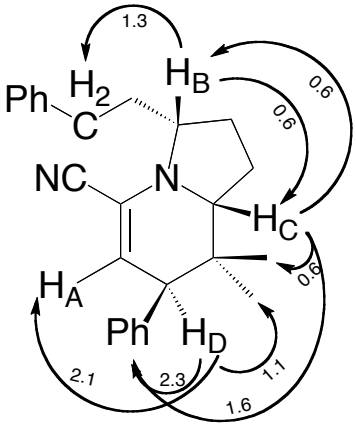
Compound **3-34**



Compound **3-35**



Compound **3-36**



Compound **3-37**

References

[1] Reviews of natural products containing indolizidine and quinolizidine: (a) Michale, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191–222. (b) Michale, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–265.

[2] Reviews of synthesis of saturated nitrogen heterocycles: (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892. (b) Ahmed, A.; Molvi, K. I.; Nazim, S.; Baig, I.; Memon, T.; Rahil, M. *J. Chem. Pharm. Res.* **2012**, *4*, 872–880.

[3] Kaneko, T.; Spande, T. F.; Garraffo, H. M.; Yeh, H. J. C.; Daly, J. W.; Andriamaharavo, N. R.; Andriantsiferana, M. *Heterocycles* **2003**, *59*, 745–757.

[4] Morita, H.; Hirasawa, Y.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 4563–4566.

[5] Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Act.* **1977**, *60*, 1128–1140.

[6] Swan, G. A. *J. Chem. Soc.* **1950**, 1534–1539.

[7] (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781–794. (c) Behforous, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259–5288. (d) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138. (e) Memeo, M. G.; Quadrelli, P. *Chem. Eur. J.* **2012**, *18*, 12554–12582.

[8] Monbaliu, J.-C. M.; Masschelein, K. G. R.; Stevens, C. V. *Chem. Soc. Rev.* **2011**, *40*, 4708–4739.

[9] (a) Perry, M. A. Ph.D. Dissertation, University of California, Irvine, 2013, pp. 1-221. (b) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035–2077 (and references therein). (c) Ahlbrecht, H.; Pfaff, K. *Synthesis* **1978**, 897–899. (d) Fang, J. M.; Chang, H. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1945–1948. (e) Fang, J. M.; Chang, H. T.; Lin, C. C. *J. Chem. Soc., Chem.*

Commun. **1988**, 1385–1386. (f) Drenkard, S.; Ferris, J.; Eschenmoser, A. *Helv*. *Chim*. *Act*. **1990**, *73*, 1373–1390.

[10] Teng, M.; Fowler, F. W. *Tetrahedron Lett*. **1989**, *30*, 2481–2484.

[11] Sisti, N. J.; Fowler, F. W.; Grierson, D. S. *Synlett* **1991**, 816–818.

[12] Sisti, N. J.; Zeller, E.; Grierson, D. S.; Fowler, F. W. *J*. *Org*. *Chem*. **1997**, *62*, 2093–2097.

[13] Motorina, I. A.; Fowler, F. W.; Grierson, D. S. *J*. *Org*. *Chem*. **1997**, *62*, 2098–2105.

[14] Motorina, I. A.; Grierson, D. S. *Tetrahedron Lett*. **1999**, *40*, 7211–7214.

[15] Motorina, I. A.; Grierson, D. S. *Tetrahedron Lett*. **1990**, *40*, 7215–7218.

[16] Tarver, J. E.; Terranova, K. M.; Joullie, M. M. *Tetrahedron* **2004**, *60*, 10277–10284.

[17] Fontaine, P.; Chiaroni, A.; Masson, G.; Zhu, J. *Org*. *Lett*. **2008**, *10*, 1509–1512.

[18] Sizemore, N. Ph.D. Dissertation, University of California, Irvine, 2014, pp. 1-191.

[19] Dr. Nicolas Sizemore obtained the results reported in the section of the chapter "Synthesis of Intermediate 3-17." Yields are from first pass reactions and were not optimized.

[20] Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M.; R. *J*. *Am*. *Chem*. *Soc*. **1970**, *92*, 741–743.

[21] Harris, J. R.; Waetzig, S. R.; Woerpel, K. A. *Org*. *Lett*. **2009**, *11*, 3290–3293.

[22] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815–3818.

[23] Shibasaki, M.; Kanai, M.; Mita, T. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, 2008; Vol. 70, pp. 1–119.

[24] Guaitierotti, J-.B.; Schumacher, X.; Wang, Q.; Zhu, J *Synthesis*, **2013**, *45*, 1380–1386.

[25] Corte, B. D.; Denis, J-. M.; Kimpe, N. D. *J*. *Org*. *Chem*. **1987**, *52*, 1147–1149.

[26] (a) Padwa, A.; Gasdaska, J. R.; Hoffmanns, G.; Rebello, H. *J. Org. Chem.* **1987**, *52*, 1027–1035. (b) Kimpe, N. D. *J. Org. Chem.* **1993**, *58*, 2904–2906.

[27] Detailed NOE correlations are found in the Experimental Section.

[28] Weyermann, P.; Keese, R. *Tetrahedron* **2011**, *67*, 3874–3880.

[29] Adachi, Y.; Kamei, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 4446–4449.

[30] Bruecher, O.; Bergstraesser, U.; Kelm, H.; Hartung, J.; Greb, M.; Svoboda, I.; Fuess, H. *Tetrahedron* **2012**, *68*, 6968–6980.

[31] Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Chem. Commun.* **2006**, 2483–2485.

[32] (a) Ansell, M. F.; Emmett, J. C.; Coombs, R. V *J. Chem. Soc.* **1968**, 217–225. (b) Blenderman, W. G.; Joullie, M. M.; Preti, G. *J. Org. Chem.* **1983**, *48*, 3206–3213.

[33] (a) Mori, K.; Sugai, T.; Maeda, Y.; Okazaki, T.; Noguchi, T.; Naito, H. *Tetrahedron* **1985**, *41*, 5307–5311. (b) Menon, S.; Sinha-Mahapatra, D.; Herndon, J. W. *Tetrahedron* **2007**, *63*, 8788–8793.

[34] Goncalves-Martin, M. G.; Saxer, A.; Renaud, P. *Synlett* **2009**, 2801–2802.

[35] Ng, S. M.; Bader, S. J.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 7315–7319.

[36] Cuellar, R. A. D. Ph.D Dissertation, University of North Carolina, Chapel Hill, 2008, pp. 1–136.

[37] Ramirez, A. P.; Thomas, A. M.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 507–510.

[38] (a) Sugawara, M.; Yoshida, J. *Tetrahedron* **2000**, *56*, 4683–4689. (b) Clive, D. L. J.; Pham, M. P. *J. Org. Chem.* **2009**, *74*, 1685–1690.

Chapter 4

DanceChemistry: A Visual Aid Teaching Tool

Abstract: A visual aid teaching tool, the DanceChemistry video series, has been developed to teach fundamental chemistry concepts through dance. These educational videos portray chemical interactions at the molecular level using dancers to represent chemical species. Students reported that the DanceChemistry videos helped them visualize chemistry ideas in a new and memorable way. Surveying the general laboratory course at the University of California, Irvine (n = 1266), 75% of the students said they wanted to use these videos to learn additional chemistry topics in the future. Data from pre- and post-surveys show an increase in students' average scores after watching a five minute DanceChemistry video. These instructional videos are disseminated broadly through a dedicated YouTube channel, DanceChemistry.

Introduction

The words "dance" and "chemistry" are not commonly used in the same sentence, but there has been a growing interest in the use of arts to teach and explain science concepts.[1] The benefits of combining the arts and science are evident when Lerman forgoes traditional classroom methods of teaching chemistry and finds that students were better engaged with more creative approaches of teaching science.[2] Kinetic theory has been taught with disco dance; it provided students with a relatable real-life activity and explained the concept using language that was appropriate to the students' level of understanding.[3] This DanceChemistry project was inspired by the increasingly popular "Dance Your Ph.D." competition started by John Bohannon. The competition encourages Ph.D. scientist to explain their dissertation project through the use of dance for the general public to understand.[4]

DanceChemistry videos are fun, memorable educational visual aids that combine fine arts and science. These videos were created with the goal of providing students with an educational resource more memorable and engaging than conventional ball-and-stick animation based representation. Because DanceChemistry videos use simplified terms and dancers to represent molecules, the videos can be incorporated into the curriculum as early as high school chemistry classes and all the way through college organic chemistry courses. Because art is often considered a universal language, these videos represent a way to educate students of many different backgrounds.

DanceChemistry videos often pair footage of real experiments with molecular-level explanations in which dancers portray individual molecules. For example, one of the DanceChemistry videos explores the concept of thin-layer chromatography (TLC). The video demonstrates how to correctly set up and develop a TLC plate. Throughout the video, viewers

examine what would be occurring on the molecular level, represented with dancers. Fourteen dancers in white makeup the TLC plate; each dancer wears a black armband to represent the plate's hydrogen bonding abilities (Figure 4-1a). Two dancers in orange are "spotted" onto the plate; one is polar and wears a black armband to represent a site of hydrogen bonding, the other one is nonpolar and does not (Figure 4-1b). Dancers in blue, representing solvent, move up the plate and push the two dancers in orange up with them (Figure 4-1c). The orange dancer with the black armband (the polar analyte) interacts with the white TLC plate dancers via dance lifts resulting in less movement up the plate and ultimately a lower R_f.

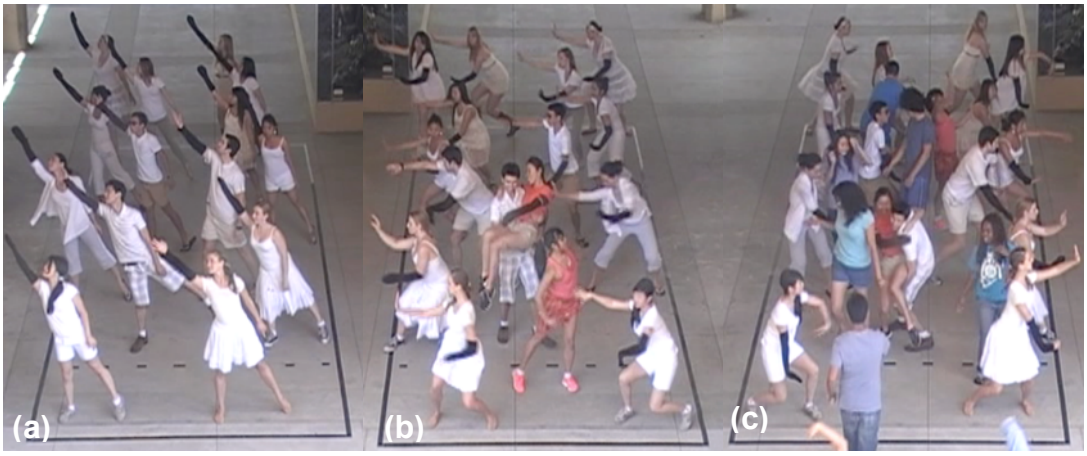


Figure 4-1. (a) TLC plate, made up of dancers in white; the black armband represents the plate's hydrogen bonding abilities. (b) Sample, represented with dancers in orange, spotted on the plate. (c) Dancers in blue represent solvent moving up the plate.

These instructional videos were not created to be substitutions for lecture, but rather a way to engage students and help visualize chemistry concepts in a different and entertaining way. DanceChemistry videos have been incorporated into the general and organic chemistry curriculum at the University of California, Irvine. They have been shown in classrooms when introducing a topic, added as supplementary links on course websites, and included as part of online homework assignments. These videos are also disseminated through the specifically

dedicated YouTube channel, DanceChemistry, and have been viewed in all fifty states in the United States and in over one hundred different countries.[5] This broad distribution could enhance the infrastructure for education at secondary schools and provide underserved communities in science with free instructional videos that can be used to improve scientific understanding from a creative viewpoint.

Results and Discussion

To measure the efficacy of the DanceChemistry videos in student learning, 1,266 undergraduate students taking general chemistry laboratory at the University of California, Irvine were surveyed. Videos covering three different topics were included in the study: thin-layer chromatography, melting point, and miscibility chromatography. The concepts of thin-layer chromatography and melting point, were unfamiliar to most students and had not been covered in class prior to this study. The concept of miscibility was discussed in a prerequisite chemistry course.

Students took a short surveys[6] on two of the chemistry topics (thin-layer chromatography, melting point, and/or miscibility) without watching any DanceChemistry videos. After four weeks, the students watched a DanceChemistry video on one of the topics and retook the same two surveys, therefore acting as a control group for the other DanceChemistry video. None of the topics were covered in lecture during the study. Each study group and control group was comprised of approximately 400 students.

Video #1: Thin-Layer Chromatography

The survey regarding thin-layer chromatography consisted of two questions.[6] The first question provided an image of a TLC plate with two spots and asked students to determine what the TLC plate would look like if it had instead been developed using a less polar solvent system.

Fifteen percent of students from the study group and 16% of students from the control group answered the question correctly (Figure 4-2). For the study group, there was a 35-percentage point increase (to 50% correct response rate) on the first question after watching the DanceChemistry video. In contrast, scores were essentially unchanged in the control group (3-percentage point correct response rate decrease). The second question on the survey asked students to rank five spots on a TLC plate in order of polarity. Twenty-two percent of students from the study group and 25% of students from the control group answered the question correctly on the pre-survey. In the post-survey, the correct response rate for the study group increased by 38-percentage points compared to an increase of only 2-percentage points in the control group. There was no significant improvement from the pre-survey to post-survey in the control group indicating that the improvement seen with the study group was solely due to the DanceChemistry video.

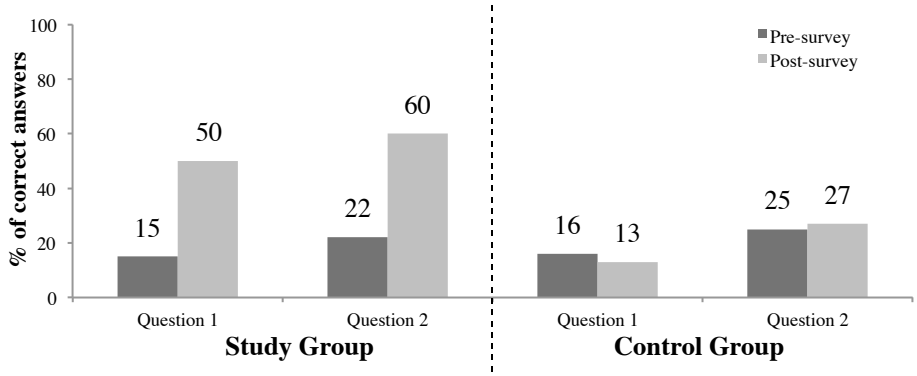


Figure 4-2. Results of the pre- and post-survey for the thin-layer chromatography DanceChemistry video

Video #2: Melting Point

The melting point survey consisted of three questions. The first question provided four images of different crystal lattice with varying degrees of impurities and asked students to rank their melting point. Less than 1% of students from the study and control groups answered the

question correctly prior to watching the video (Figure 4-3). The study group improved by 27-percentage points on the post-survey; there was no improvement in the control group. The second question on the survey asked students to determine which of several statements were true about a mixed melting point experiment. There was a 36-percentage point improvement with the study group on the post-survey. The third question on the survey probed the relationship of stack ability of a compound and its melting point. On the pre-survey, 9% of students in the study group and 8% of the students in the control group answer this question correctly. After watching the video, there was a 24-percentage point increase with the study group. Similar to the thin-layer chromatography video study, there was no significant improvement on any of the questions on the pre- to post-survey for the control group.

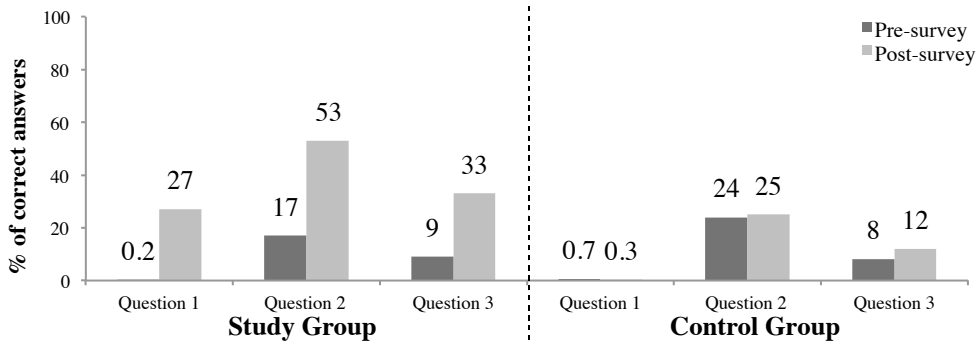


Figure 4-3. Results of the pre- and post survey for the melting point DanceChemistry video

Video #3: Miscibility

A survey with four multiple choice questions about ΔG, ΔH, and ΔS was given to the students to measure the efficacy of the miscibility DanceChemistry video. Sixty four percent of students from the study group and 57% from the control group correctly answered the first question about ΔG when two liquids are miscible (Figure 4-4). Ninety-six percent of students in the study group answered the question correctly in the post-survey, a 32-percentage point

increase. For the second question involving the entropy of a solution, there was a 35-percentage point improvement with the study group on the post-survey. For the third question regarding ΔH of a reaction, a large majority of students in both groups provided the correct answer. There was no noteworthy difference from the pre- and post-survey because the pre-survey correct response rate was nearly 100%. The survey also asked students to indicate if they guessed the answer to the question. On the pre-survey, 35% of students in the study group and 26% of students in the control group admitted to guessing the correct answer. On the post-survey, only 1% of students in the study group admitted to guessing the correct answer while 18% of students in the control group still obtained the correct answer simply though guessing. Therefore, even though average student scores were unchanged, the DanceChemistry videos helped students gain confidence in their knowledge of the subject. The fourth question probed conditions when liquids are miscible; there was a 14-percentage point increase when comparing the pre- and post-survey for the study group. There was no significant difference (>10-percentage point increase) for the control group when comparing the pre- and post-survey for all four quiz questions, again indicating that the increased number of correct answers received from the study group was due exclusively to the DanceChemistry video.

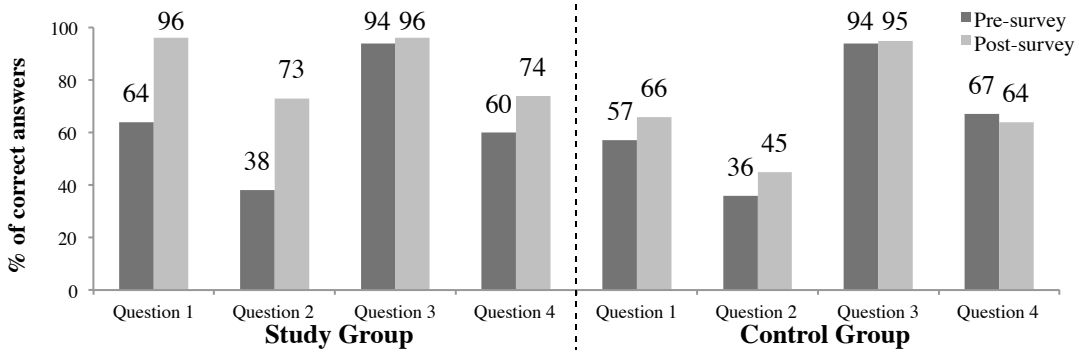


Figure 4-4. Results of the pre- and post-survey for the miscibility DanceChemistry video

Overall, there was a smaller improvement when comparing the pre- and post-survey of the miscibility video than with the thin-layer chromatography and melting point video. This is probably due to the fact that the students had previously learned about miscibility before being exposed to the DanceChemistry video. Nevertheless, the improvement in all three cases suggests these videos can be used to introduce a topic or as a supplementary learning tool after a topic has already been introduced in a conventional manner.

To ensure the DanceChemistry videos were not too abstract for students, the post-survey also asked students to correctly identify what a specific dancer represented. For the thin-layer chromatography video, only 66% of the students correctly answered the question, but for the melting point and miscibility videos, 96% and 92% of students provided the correct answer, respectively. The lower correct response for the thin-layer chromatography video may be due to the fact that the topic of TLC has many components and is inherently a topic many students struggle with. This data suggest that not all chemistry topics can be easily transformed into DanceChemistry videos.

For the three videos, 79% (thin-layer chromatography), 85% (melting point), and 78% (miscibility) of students stated that they felt they had a better understanding of the topic after watching the DanceChemistry visual aid. Of the 1266 students surveyed, 75% of them said they wanted to use DanceChemistry videos to learn additional chemistry topics in the future. Many of the students commented on the engaging nature of the videos. Below are a few select statements.

- "It was a visual representation of how it works. Students whom [sic] are visual learners will appreciate this style of teaching."
- "It was an excellent way to visualize the process. Every note was thoroughly addressed and understood."
- "The video was both educational and entertaining."
- "The video grabbed my attention better than traditional classroom setting would have."

- "It was entertaining and got me more excited for the topic."
- "The video was silly but that is why I'll remember the information. It was helpful."
- "The video is interesting. It makes chemistry easy."
- "It was a very random way to teach a lesson but because it is so absurd and usual, I wont forget it."

Future Project: More DanceChemistry Videos

I created the videos described within this chapter, but recently there have been three more DanceChemistry videos created in collaboration with a team of eight undergraduate and graduate students in the dance, chemistry, and education departments. Currently the efficacy of these three videos are being examined in the organic chemistry laboratory course (Chem 51LC), the general chemistry laboratory course (Chem 1LC), and the general chemistry lecture course (Chem 1C). More DanceChemistry videos will be created, in the future, in collaboration with the performing arts department at Rockford University. These educational videos could eventually span outside the field of chemistry into other physical and biological sciences.

Conclusion

This study demonstrated that the DanceChemistry videos are an effective way to introduce or supplement a chemistry topic. Students enjoyed the videos and their understanding of topic covered improved. To date, ten DanceChemistry videos have been created covering the topics: thin-layer chromatography, melting point, miscibility, relationship between temperature and pressure, solvent dependency of fluoride as a nucleophile, recrystallization, solubility, distillation, rate laws, and acid base titration.

References

[1] (a) Irving, L. T. Teaching Statistics Using Dance and Movement *Front. Psychol.* [Online] **2015**, *6* http://journal.frontiersin.org/article/10.3389/fpsyg.2015.00050/full#B5 (accessed Feb 17, 2015). (b) Grabel, L.; Weir. M.; Appel, L. F.; Johnson, E.; McCarthy, R.; Lerman, L. *CBE Life Sci. Educ.* **2013**, *12*, 582–583. (c) Burke, J. S. Chemistry Meets Choreography to Enhance Student Comprehension *Edutopia* [Online] **2009**, http://www.edutopia.org/arts-education-chemistry-dance-visualization (accessed Feb 17, 2015).

[2] Z. M. *J. Chem. Ed.* **2003**, *80*, 1234–1242.

[3] Karakas, M. *J. Chem. Ed.* **2010**, *87*, 928–930.

[4] More information about the Dance Your Ph.D. competition can be found at: Gonzolabs.org/dance

[5] The DanceChemistry Videos can be watched at: youtube.com/user/DanceChemistry

[6] Survey questions can be found in the Appendix

APPENDIX

Biological Testing of Synthetic and Naturally Occurring Cyanolide A

Report from the Gerwick group, written by Dr. Karin Kleigrewe
All data within this report was obtained by Dr. Karin Kleigrewe

Molluscicide activity of cyanolide A

Cyanolide A, a glycosidic macrolide, was isolated from a Papua New Guinea collection of *Lyngbya bouillonii* and showed strong molluscicidal activity. Cyanolide A analogs which were synthesized in a lab at UC Irvine were submitted to the molluscicide assay in our lab (data unpublished). However neither the synthetic cyanolide A nor their analogs demonstrated any molluscicidal activity. So my task was to find the reason for the contradictory activity. Is the synthetic cyanolide A the same compound as the isolated cyanolide A? And if yes, does another compound cause the molluscicidal activity?

Around 0.5 mg of the isolated cyanolide A and around 10 mg of the synthetic cyanolide A were available.

To begin, ^{1}H-NMR data were recorded for both compounds in *d*-chloroform on a 600 MHz NMR with cryoprobe. Both samples show mostly the same chemical shifts. Nevertheless the isolated cyanolide A (red trace, Figure A-1) also has some impurities at the chemical shift between 0.5 and 2 ppm. The isolated cyanolide A was therefore repurified by preparative HPLC.

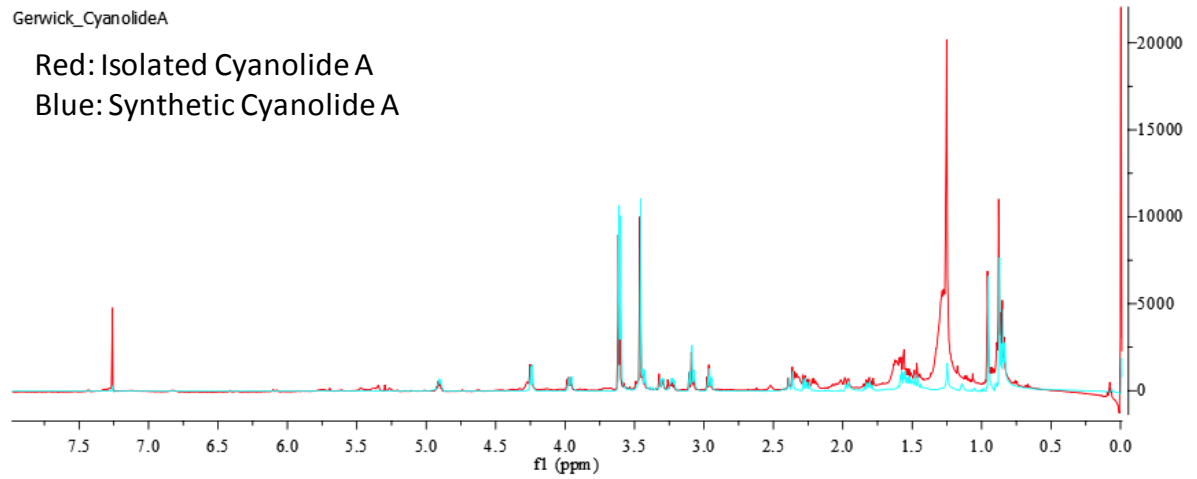


Figure A-1: ^{1}H-NMR comparison between the isolated cyanolide A and the synthetic cyanolide A. The ^{1}H-NMR was recorded in $CDCl_3$ on a 600 MHz NMR with cryoprobe.

Because of the low amount of the isolated cyanolide A, the isolation method was first developed with the synthetic analog. The original publication used two columns in series (Phenomenex Luna 10 μm silica 100 Å, 250 x 4.6 mm) with 40% ethyl acetate and 60% hexanes as eluents and a flow rate of 1.5 mL/min. Because of the low amount of sample, cyanolide A was not detectable by UV-detection. Therefore, fractions were collected and each fraction was measured by HPLC-MS/MS. Unfortunately, it turned out that with the published method cyanolide A elutes in a time range from 17-27 min. Since the normal phase separation did not show the desired results, a reversed phase HPLC method was developed. Chromatographic separation was carried out on a Synergi 4u Fusion-RP 80A, 250 x 4.6 mm, 4 micron, Phenomenex column using a binary gradient. The flow rate was set to 1 mL/min. Solvent A was acetonitrile and solvent B was water. The gradient was programmed as

follows: 0 min 50% A, 35 min 100% A, 40 min 100% A, 41 min 50% A, 46 min 50% A. Cyanolide A elutes between 24 and 25 min. Figure A-2 shows the chromatogram of the synthetic cyanolide A at 210 nm.

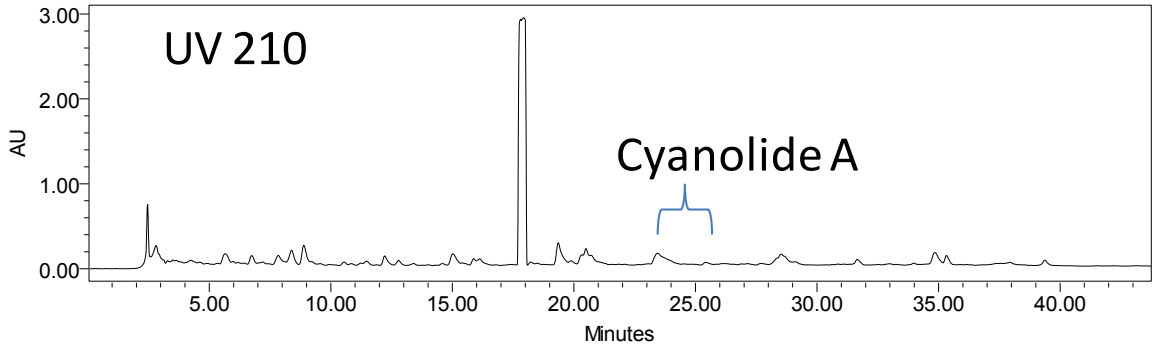


Figure A-2: RP-HPLC-UV chromatogram of the synthetic cyanolide A.

The isolated cyanolide A was then purified with the same method. Figure A-3 shows the HPLC-UV chromatogram. This cyanolide A was present in fraction 24 min and 25 min both were pooled together.

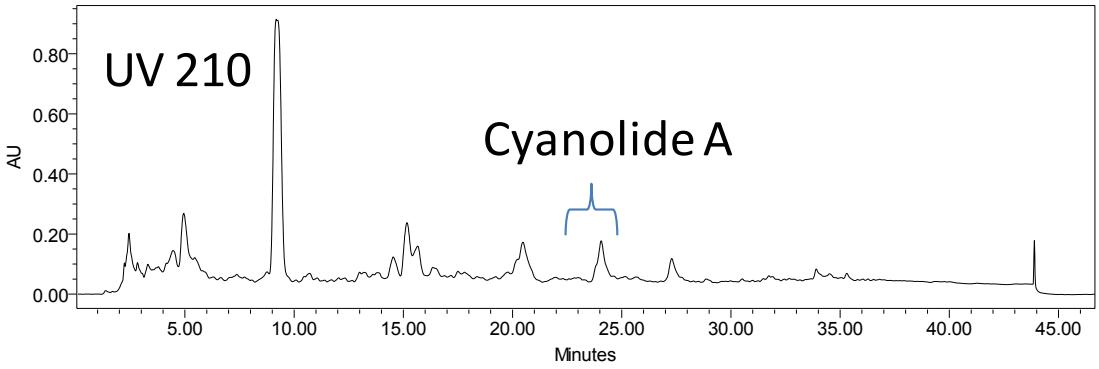


Figure A-3: RP-HPLC-UV chromatogram of the isolated cyanolide A.

The isolated and synthetic cyanolide A were again measured by ^{1}H-NMR. Figure A-4 shows the ^{1}H-NMR spectra. Compared to Figure A-1 this NMR looks more pure.

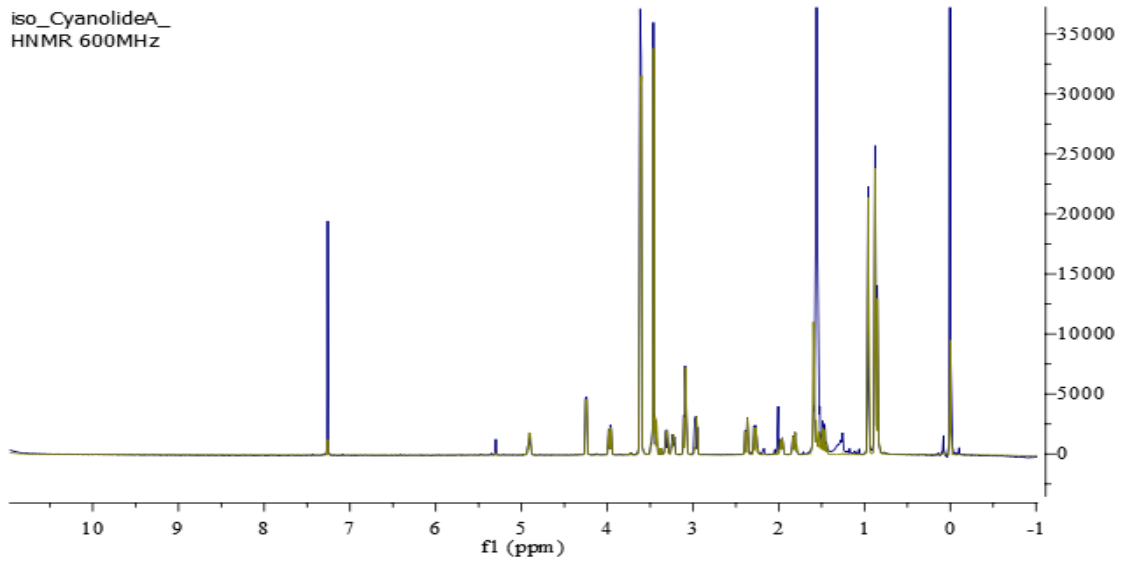


Figure A-4: ^{1}H-NMR of purified cyanolide A.

Next, the bioactivity of the collected fractions was tested in the molluscicide assay again. As positive control barbamide with a concentration of 1 μg/mL was used. The negative control was ethanol which was used for the dilution of the fractions. The dilutions for the assay were calculated so that each fraction contained around the LC_{50}=1.2 μM (7 μg per 7 mL) of cyanolide A. Due to the high molluscicidal activity these levels should be sufficient to see effects and will not waste the remaining pure compound. The remaining material will be needed for further structural elucidation. First, all fractions except the fractions containing cyanolide A (24 min and 25 min) were tested. Interestingly, one snail out of two died in the 23 min fraction (Table A-1). This experiment was repeated with the 23 min fraction. After 24 h both snails were alive but after 48 h both were dead. Since trace amounts of cyanolide A were detectable with HPLC-HRMS, the experiment was repeated with the pooled sample of 24 min and 25 min to confirm the activity of this fraction. After 48 h hours both snail were still alive.

Table A-1: Molluscicidal activity of the isolated fractions.

Fraction	Amount	snails
0-4 min	0.1 mg	2 alive
4-8 min	0.07 mg	2 alive
8-12 min	0.21 mg	2 alive
12-16 min	0.21 mg	2 alive
16-19 min	0.17 mg	2 alive
19-21 min	0.19 mg	2 alive
22 min	0.2 mg	2 alive
23 min	0.04 mg	1 dead, 1 alive
24 min	0 mg	not tested
25 min	0.06 mg	not tested
26 min	0.16 mg	2 alive
27 min	0.09 mg	2 alive
28 min	0.11 mg	2 alive
29 min	0.05 mg	2 alive
30 min	0.08 mg	2 alive
31 min	0.05 mg	2 alive
32 min	0.04 mg	2 alive
32-34 min	0.04 mg	2 alive
32-34 min	0.04 mg	2 alive
34-36 min	0.11 mg	2 alive
Syn Cyanolide	0.51 mg	2 alive
Control	0.07 mg	2 alive
Barbamide	35 μL of 20 mg/mL	2 dead

Additionally, a ^{1}H-NMR was recorded of the 23 min fraction. Clearly another compound other than cyanolide A is present in this sample (Figure A-5). Unfortunately, the sample amount is so low that it is difficult to obtain any further spectroscopic data. So the next steps of this project will be to find further unpurified material of this fraction and to try to get as much structural information with the amount of sample we have at the moment.

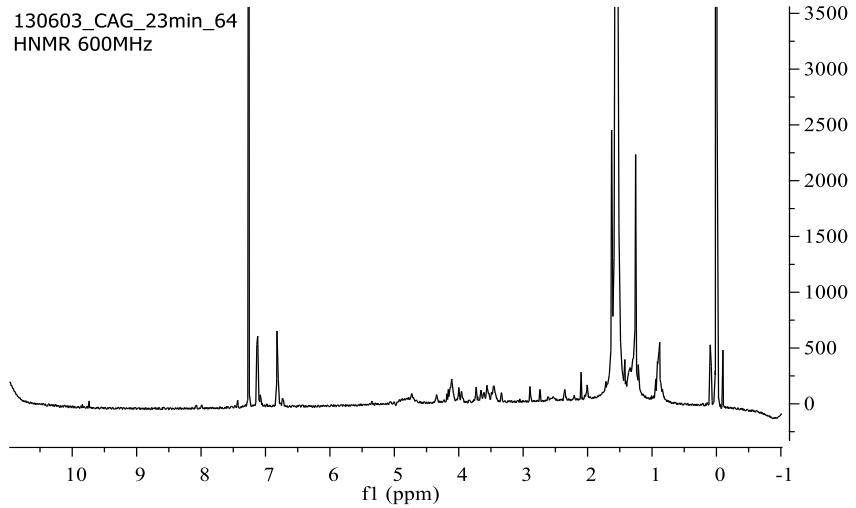
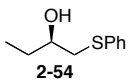


Figure A-5: ^{1}H-NMR of 23 min fraction (recorded in $CDCl_3$ on a 600 MHz NMR).

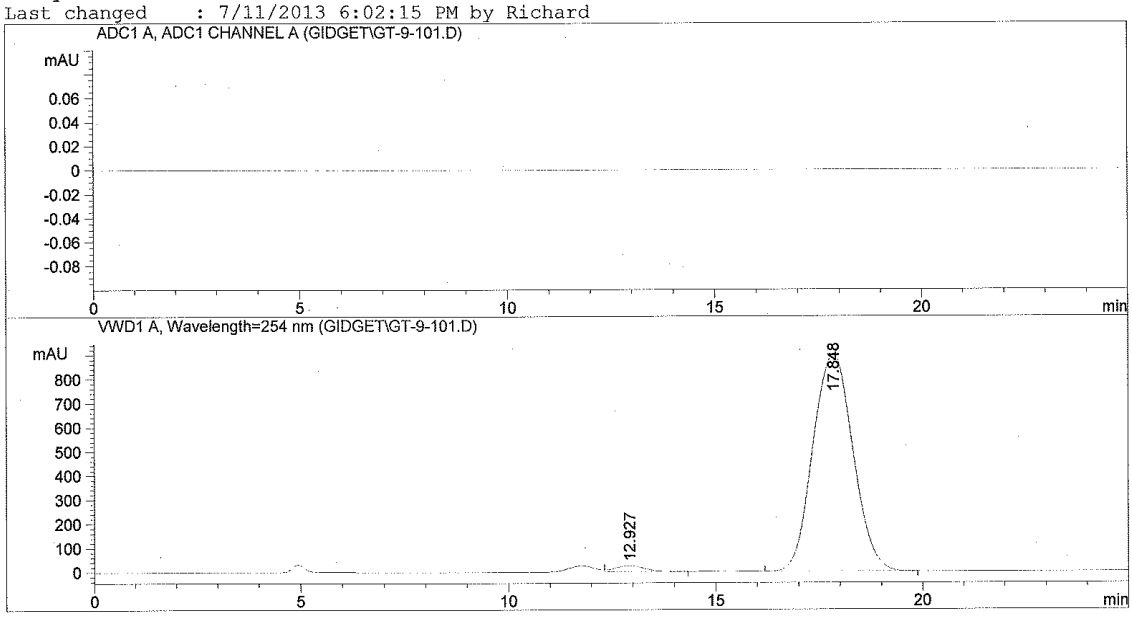
Data File C:\HPCHEM\1\DATA\GIDGET\GT-9-101.D Sample Name: GT-9-101-OH

Chiralcel AD with AD guard 5% iPrOH/n-Hexane 1.0 mL/min
24 bar 254 NM UV



2-54

```
Injection Date  : 7/16/2013 4:21:43 PM
Sample Name     : GT-9-101-OH                    Location : Vial 32
Acq. Operator   : Gidget
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\ALEX.M
Last changed    : 7/16/2013 4:20:37 PM by Gidget
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ALEX.M
Last changed    : 7/11/2013 6:02:15 PM by Richard
```



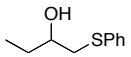
Area Percent Report

```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :     50.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: ADC1 A, ADC1 CHANNEL A


Signal 2: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.927 VP    0.7762 1231.96997   25.17413   1.9960
   2  17.848 VB    1.0735 6.04907e4   902.06409  98.0040

Totals :                  6.17226e4   927.23822

 Results obtained with enhanced integrator!
```

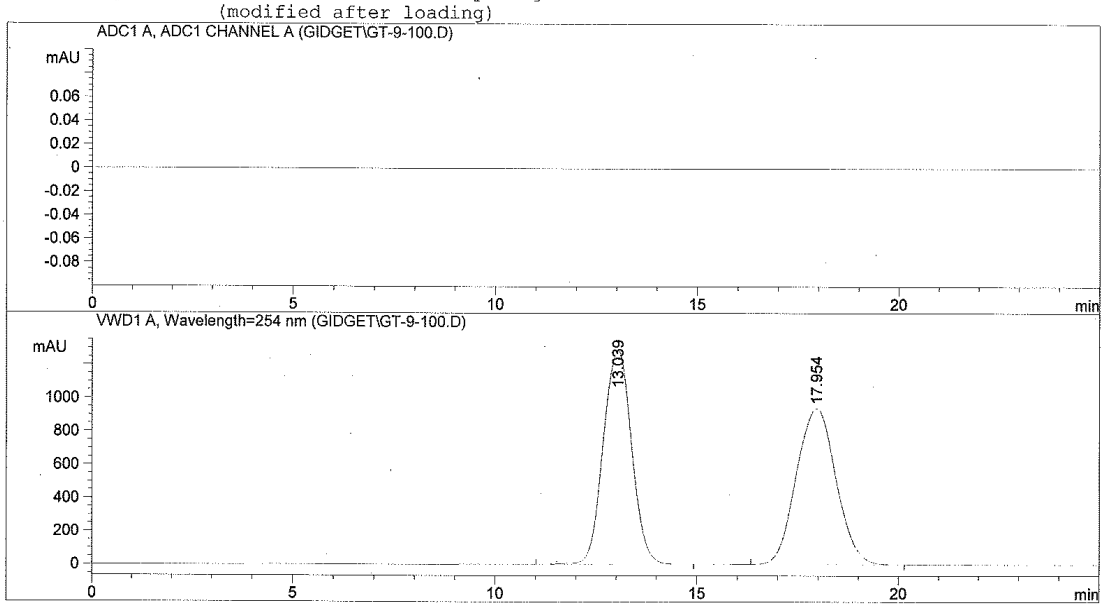
*** End of Report ***

Data File C:\HPCHEM\1\DATA\GIDGET\GT-9-100.D Sample Name: GT-9-100-RAC

Chiralcel AD with AD guard 5% iPrOH/n-Hexane 1.0 mL/min
24 bar 254 NM UV




```
Injection Date  : 7/16/2013 3:54:38 PM
Sample Name     : GT-9-100-RAC                    Location : Vial 31
Acq. Operator   : Gidget
                                                  Inj Volume : 10 µl
Method          : C:\HPCHEM\1\METHODS\ALEX.M
Last changed    : 7/16/2013 4:16:33 PM by Gidget
                  (modified after loading)
```

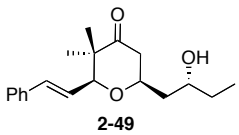



```
                          Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :     50.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: ADC1 A, ADC1 CHANNEL A


Signal 2: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
   1  13.039 BB    0.7630 6.27346e4  1285.43958  49.4910
   2  17.954 BB    1.0769 6.40251e4   936.83740  50.5090

Totals :                  1.26760e5  2222.27698

 Results obtained with enhanced integrator!

                          *** End of Report ***
```

1100 LC 7/16/2013 4:19:47 PM Gidget Page 1 of 1

Data File C:\HPCHEM\1\DATA\GIDGET\G-4-52A.D Sample Name: GT-4-52-ALC

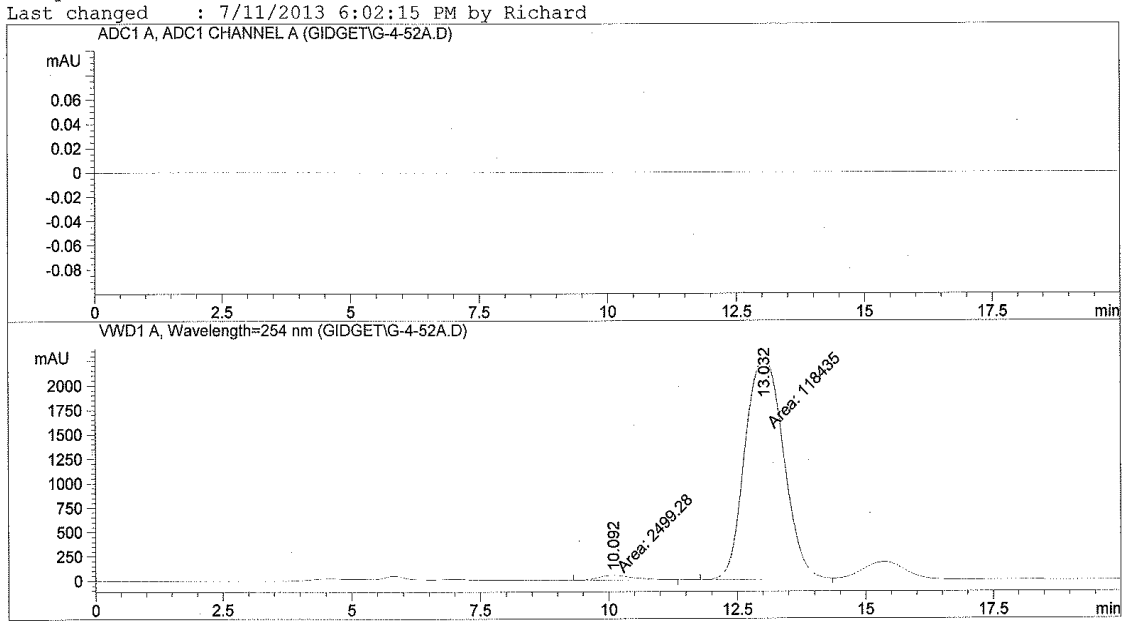
Chiralcel AD with AD guard 10% iPrOH/n-Hexane 1.0 mL/mi
n 24 bar 254 NM UV



2-49

Injection Date : 7/17/2013 12:26:52 AM
Sample Name : GT-4-52-ALC Location : Vial 34
Acq. Operator : Gidget
Inj Volume : 10 µl

Acq. Method : C:\HPCHEM\1\METHODS\ALEX.M
Last changed : 7/17/2013 12:25:01 AM by Gidget
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ALEX.M
Last changed : 7/11/2013 6:02:15 PM by Richard



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 50.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.092	MM	0.8357	2499.27881	49.84238	2.0666
2	13.032	MM	0.8726	1.18435e5	2262.23462	97.9334
Totals :				1.20935e5	2312.07700	

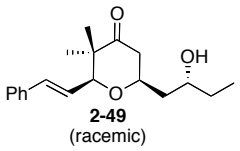
Results obtained with enhanced integrator!

*** End of Report ***

1100 LC 7/17/2013 12:48:30 AM Gidget Page 1 of 1

Data File C:\HPCHEM\1\DATA\GIDGET\G-4-52R.D Sample Name: GT-4-52-RAC

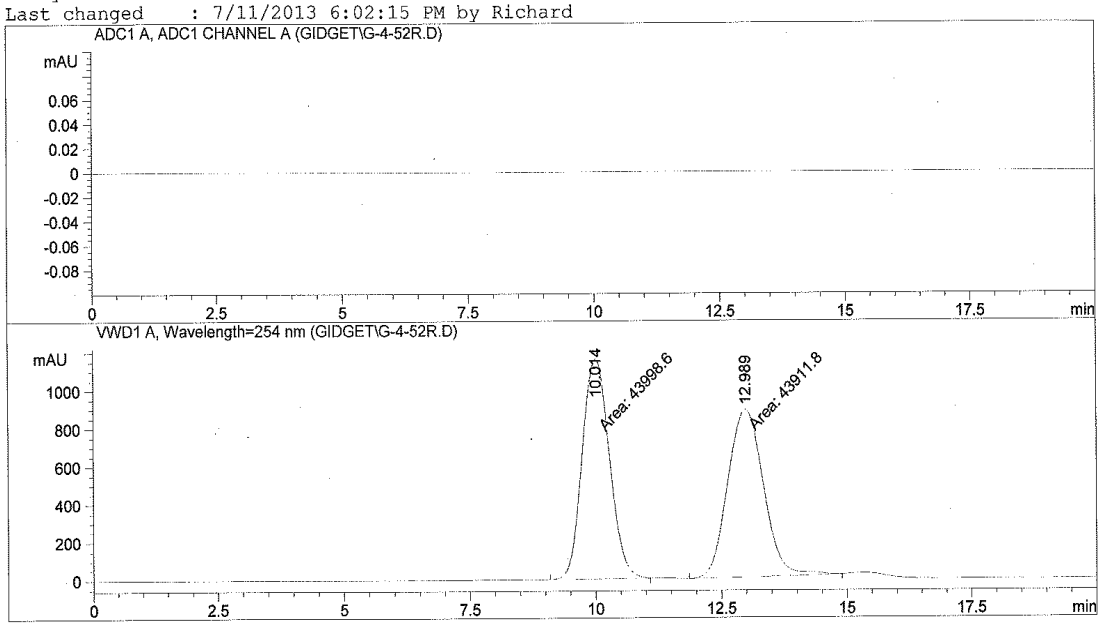
Chiralcel AD with AD guard 10% iPrOH/n-Hexane 1.0 mL/mi
n 24 bar 254 NM UV



2-49
(racemic)

Injection Date : 7/17/2013 12:05:02 AM
Sample Name : GT-4-52-RAC Location : Vial 33
Acq. Operator : Gidget
Inj Volume : 10 µl

Acq. Method : C:\HPCHEM\1\METHODS\ALEX.M
Last changed : 7/17/2013 12:25:01 AM by Gidget
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ALEX.M
Last changed : 7/11/2013 6:02:15 PM by Richard



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 50.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.014	MM	0.6320	4.39986e4	1160.32141	50.0494
2	12.989	MM	0.8262	4.39118e4	885.86011	49.9506

Totals : 8.79105e4 2046.18152

Results obtained with enhanced integrator!

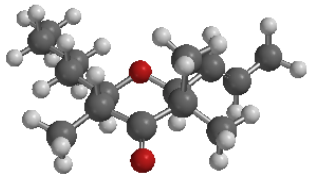
*** End of Report ***

1100 LC 7/17/2013 12:27:52 AM Gidget

Calculated Geometries and Energies

The B3LYP/61-3G(d) optimized geometry and energies of THPO **2-74**, **2-75***c*, and **2-75***t* are given below.

THP 2-74

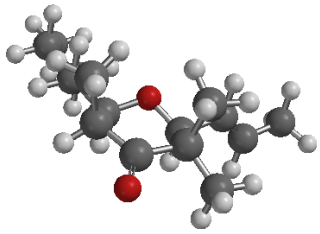


C	0.057810	-2.092253	-0.181442
C	-2.066250	-0.556354	-0.242417
C	-1.420496	-1.891854	0.174822
C	-1.086684	0.581572	0.210812
C	0.847298	-0.822998	0.238046
H	-1.050040	0.562758	1.313813
H	0.828990	-0.754245	1.341770
O	0.223372	0.338602	-0.303657
O	-2.050531	-2.744635	0.774576
C	-1.482841	1.960133	-0.237166
H	-1.388043	2.156205	-1.304811
C	-1.911764	2.923798	0.581605
H	-1.983122	2.712352	1.650294
C	-2.315067	4.305918	0.156285
H	-1.704681	5.067214	0.660221
H	-3.359656	4.514469	0.423998
H	-2.207172	4.442917	-0.924729
C	2.300696	-0.813478	-0.236021
H	2.308574	-0.903092	-1.331847
H	2.805426	-1.703897	0.158761
C	3.073474	0.442051	0.188811
H	3.039857	0.536219	1.284915
H	2.564278	1.326739	-0.210543
C	4.536022	0.429889	-0.272486
H	4.569808	0.316489	-1.365595
H	5.042677	-0.454700	0.140110
C	5.302205	1.692926	0.133429
H	6.343245	1.657614	-0.207693
H	5.312780	1.816944	1.223405
H	4.839835	2.590065	-0.296045
C	-2.242528	-0.554627	-1.779403
H	-1.281257	-0.517838	-2.300362
H	-2.830992	0.314737	-2.091915
H	-2.781174	-1.451954	-2.104704
C	-3.428104	-0.400674	0.445332
H	-4.096741	-1.218230	0.162733
H	-3.888426	0.550097	0.160757
H	-3.329369	-0.426290	1.535996
H	0.120719	-2.139660	-1.279373

C	0.604905	-3.390475	0.417352
H	1.598843	-3.619513	0.022871
H	-0.061986	-4.225116	0.188191
H	0.673086	-3.322318	1.509079

E(scf) = –737.696198 au

THP 2-75*c*

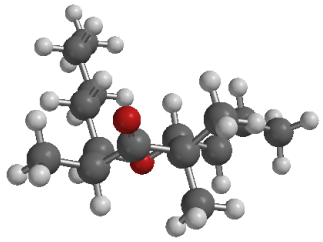


C	0.015979	-2.154152	0.194819
C	-2.077043	-0.513691	0.036274
C	-1.472840	-1.876195	0.452244
C	-1.008755	0.610665	0.242163
C	0.846260	-0.867097	0.394323
H	-0.884859	0.754484	1.329457
H	0.824302	-0.625213	1.472786
O	0.248027	0.217553	-0.315403
O	-2.172505	-2.743610	0.943861
C	-1.362635	1.933237	-0.380910
H	-1.268972	1.984759	-1.465237
C	-1.751435	3.011393	0.304211
H	-1.820780	2.946536	1.391698
C	-2.106639	4.338677	-0.301002
H	-1.461458	5.136165	0.091410
H	-3.139201	4.623978	-0.058115
H	-2.005445	4.325093	-1.391348
C	2.308593	-0.958017	-0.041966
H	2.349403	-1.100929	-1.129323
H	2.752990	-1.855420	0.412057
C	3.124938	0.283487	0.338962
H	3.107756	0.412303	1.431855
H	2.633983	1.168505	-0.083608
C	4.580325	0.220355	-0.140199
H	4.595916	0.073314	-1.229720
H	5.070321	-0.664028	0.292381
C	5.383888	1.475603	0.214203
H	6.417110	1.403643	-0.144401
H	5.418109	1.632782	1.299274
H	4.935722	2.370290	-0.235144
C	-2.483212	-0.616162	-1.454426
H	-1.608431	-0.654779	-2.109048
H	-3.080574	0.256816	-1.738121
H	-3.091805	-1.510220	-1.625936
C	-3.322188	-0.232750	0.891068

H	-4.059655	-1.028278	0.761967
H	-3.771642	0.721548	0.599998
H	-3.073388	-0.186415	1.957662
H	0.304472	-2.883269	0.962523
C	0.202357	-2.830221	-1.180351
H	1.209944	-3.248674	-1.267172
H	0.056548	-2.128267	-2.006142
H	-0.512199	-3.651711	-1.292684

E(scf) = –737.691739 au

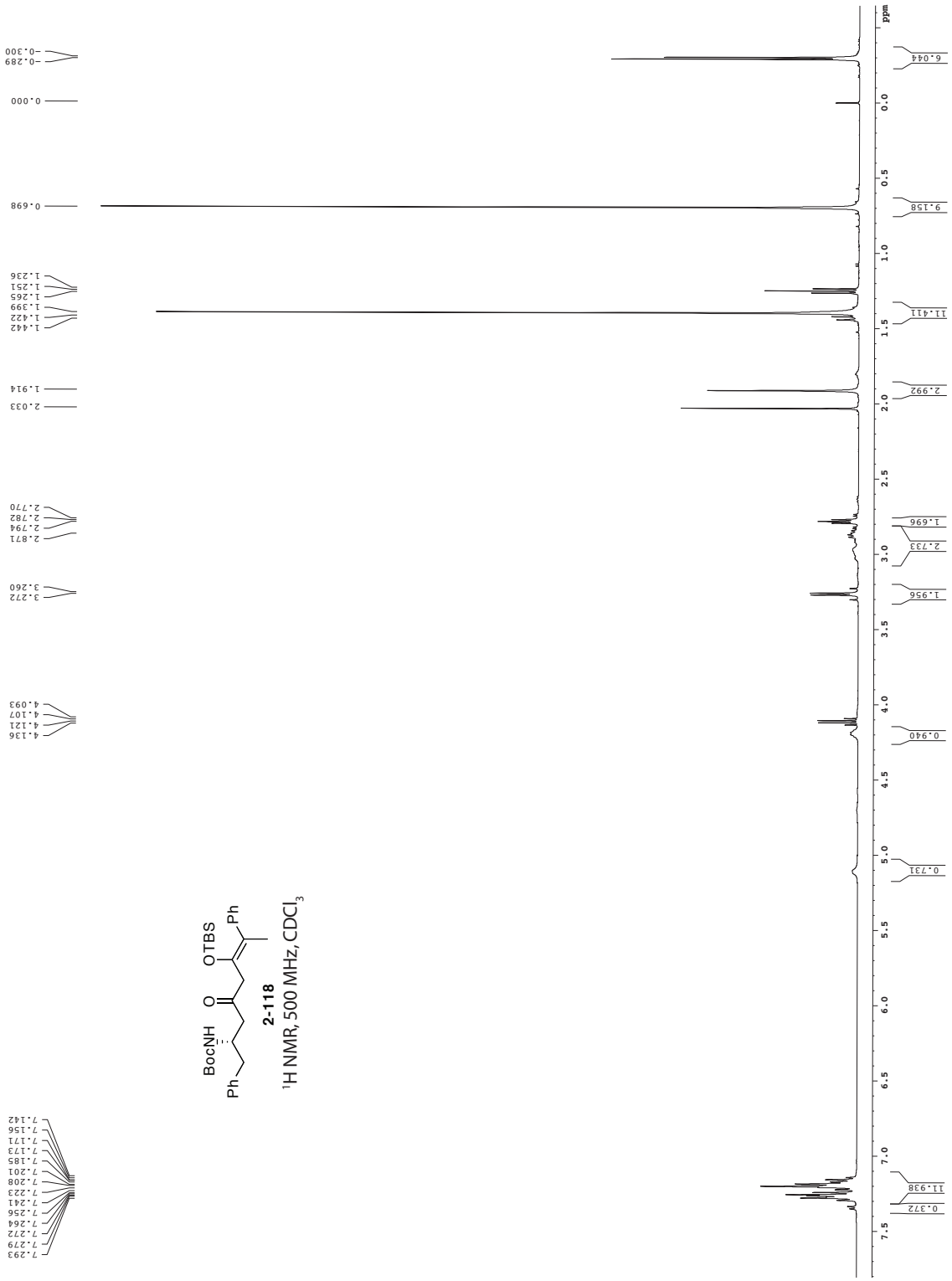
THP 2-75*t*

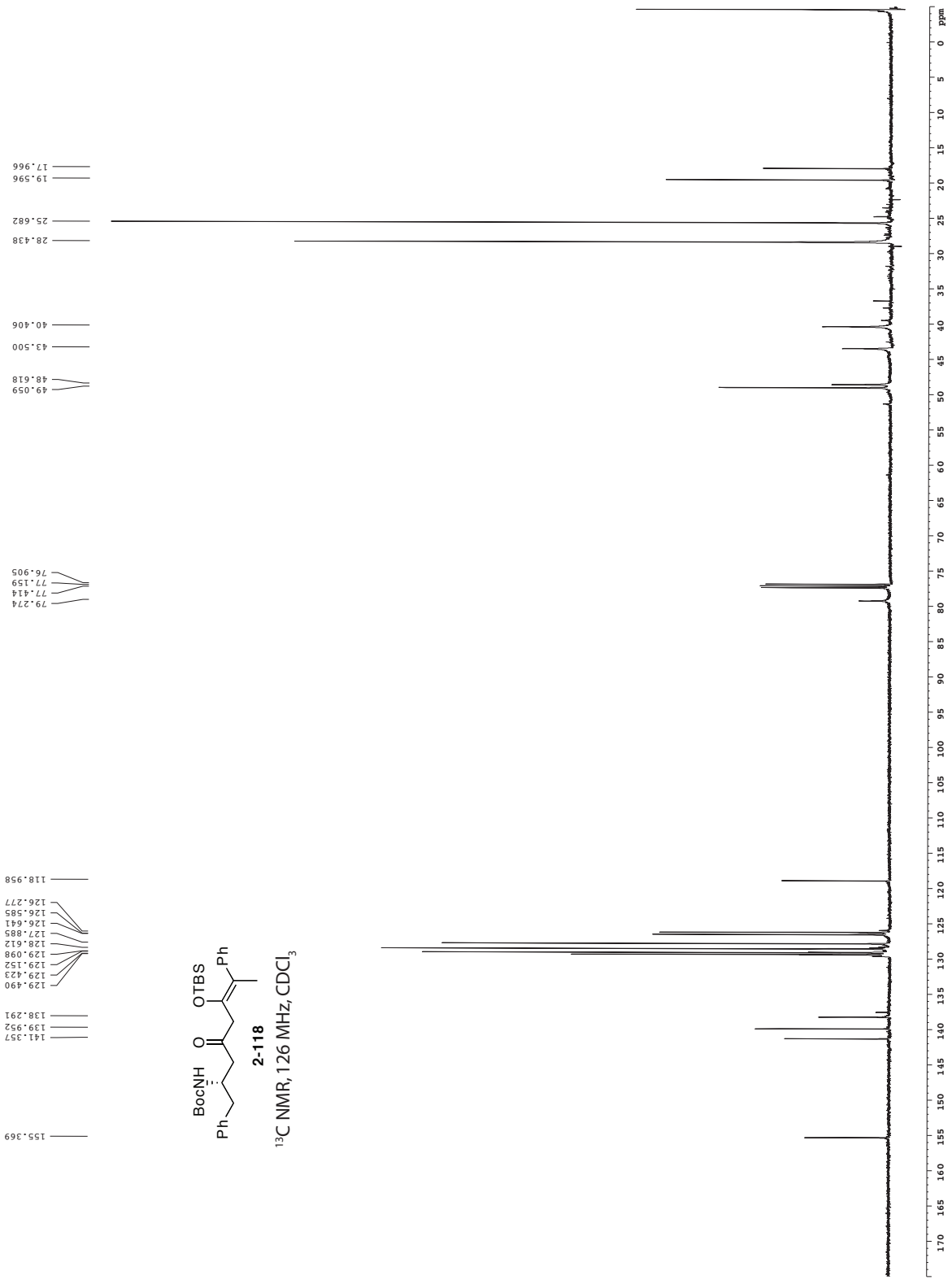


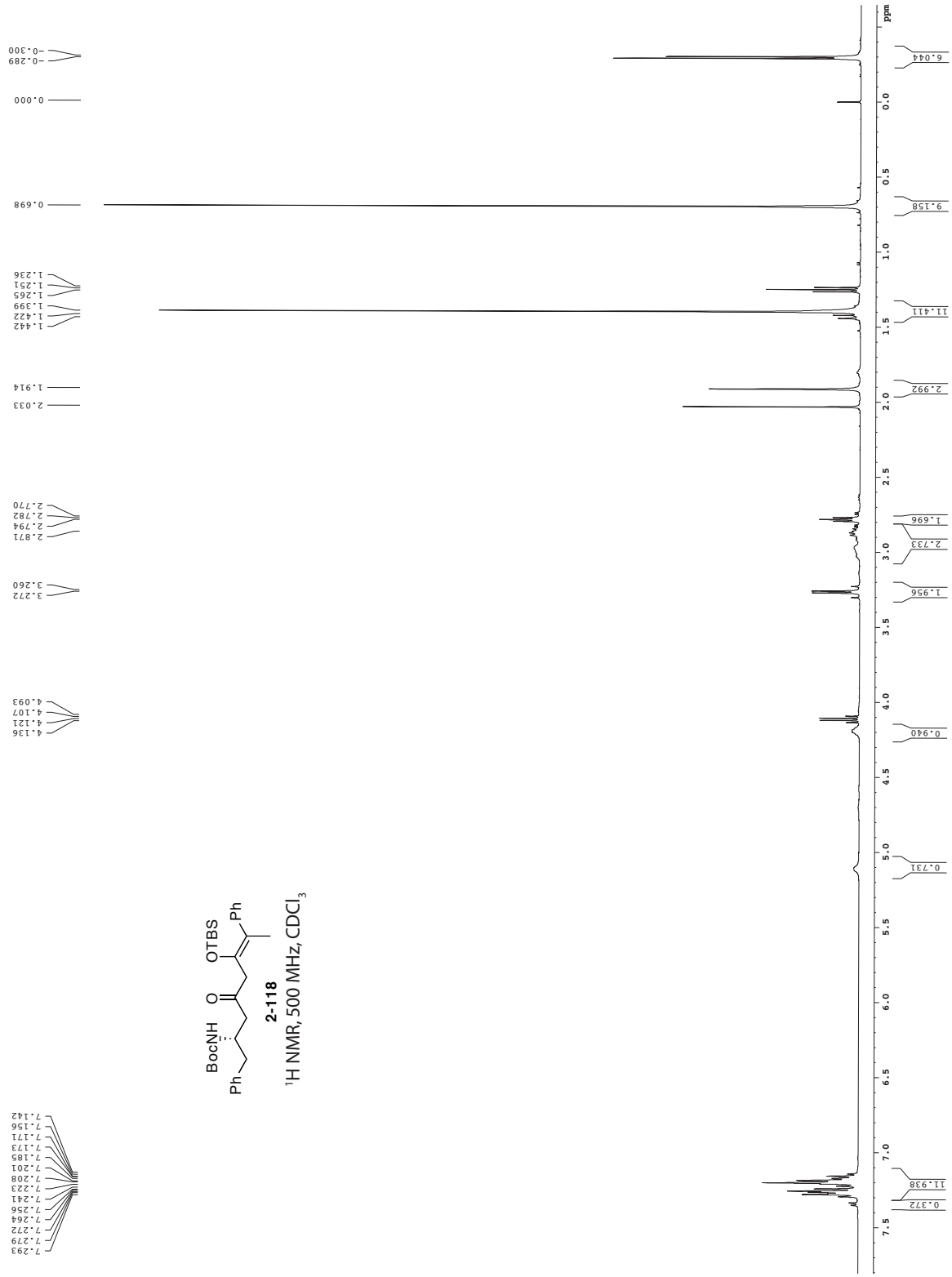
C	-0.503615	-2.179407	0.678747
C	-1.926149	-0.220051	-0.276030
C	-1.367388	-1.644047	-0.461168
C	-0.716194	0.696428	0.130066
C	0.606530	-1.136758	0.997774
H	1.049399	-1.397706	1.966881
O	0.001413	0.138538	1.235856
O	-1.587726	-2.299284	-1.464634
C	-1.107204	2.085456	0.552274
H	-1.577347	2.163501	1.531945
C	-0.900238	3.185203	-0.176383
H	-0.410685	3.088693	-1.147374
C	1.738828	-1.081432	-0.039552
H	1.333451	-0.927918	-1.049807
H	2.218910	-2.067788	-0.061626
C	2.793072	-0.010105	0.266636
H	3.192523	-0.174793	1.278496
H	2.316401	0.977903	0.291018
C	3.949514	-0.004035	-0.740560
H	3.549080	0.152128	-1.752655
H	4.425297	-0.995039	-0.753404
C	5.004844	1.065075	-0.439543
H	5.817728	1.043713	-1.174472
H	5.448639	0.915845	0.552552
H	4.567124	2.070821	-0.456051
C	-2.550628	0.265025	-1.590077
H	-1.825588	0.239795	-2.410570
H	-2.919318	1.289893	-1.482992
H	-3.384743	-0.381435	-1.877029
C	-2.996798	-0.250573	0.841241
H	-3.737471	-1.033481	0.642229
H	-3.528950	0.705628	0.878037

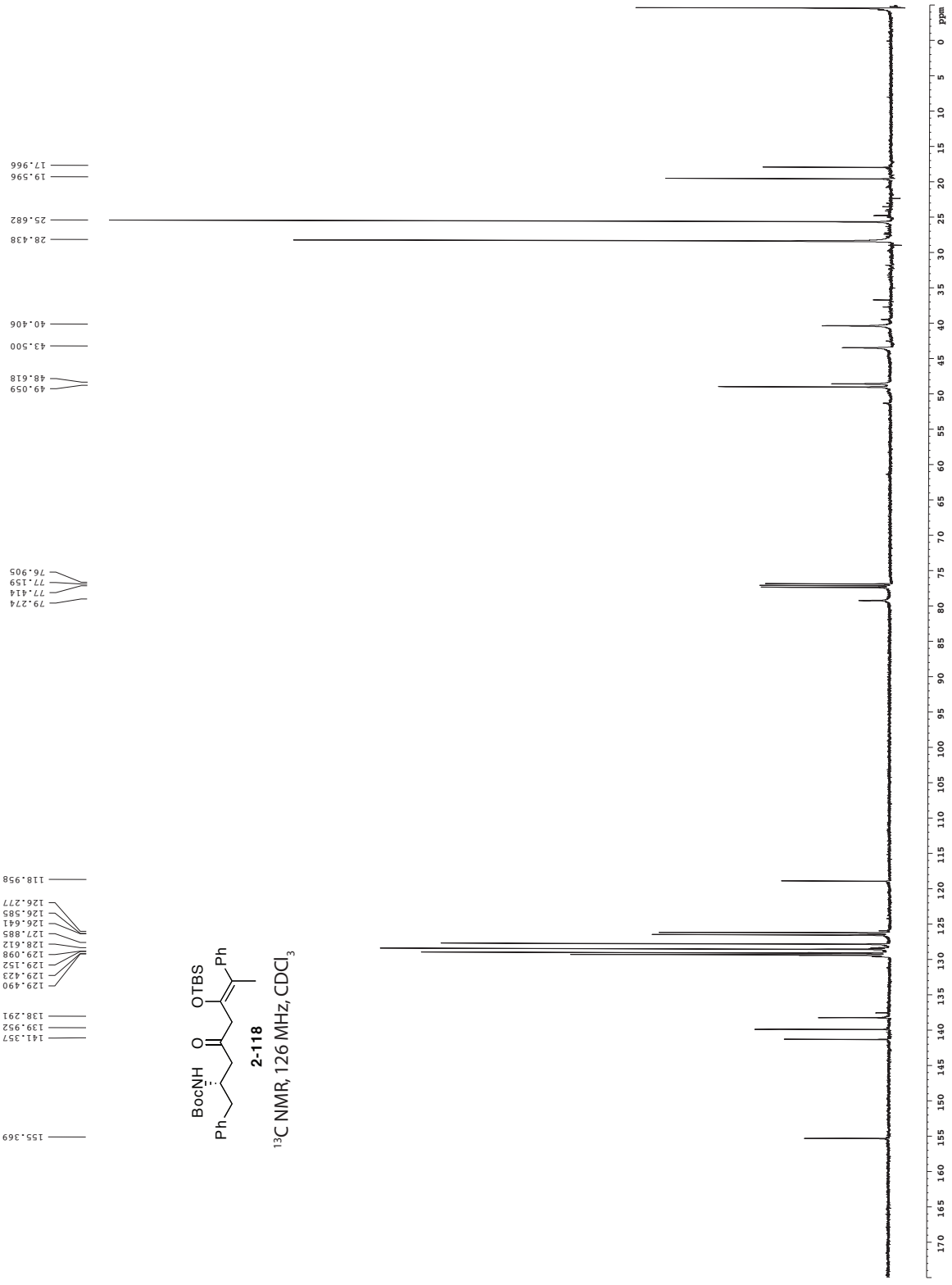
H	-2.554759	-0.430484	1.825351
H	-1.141455	-2.196324	1.573562
C	0.006884	-3.596304	0.411773
H	0.648457	-3.938854	1.232298
H	0.572113	-3.652925	-0.522254
H	-0.832188	-4.292150	0.320274
H	-0.058067	0.770535	-0.748990
C	-1.289787	4.576868	0.231189
H	-1.984828	5.023253	-0.492719
H	-0.412835	5.236792	0.271118
H	-1.769720	4.587838	1.215347

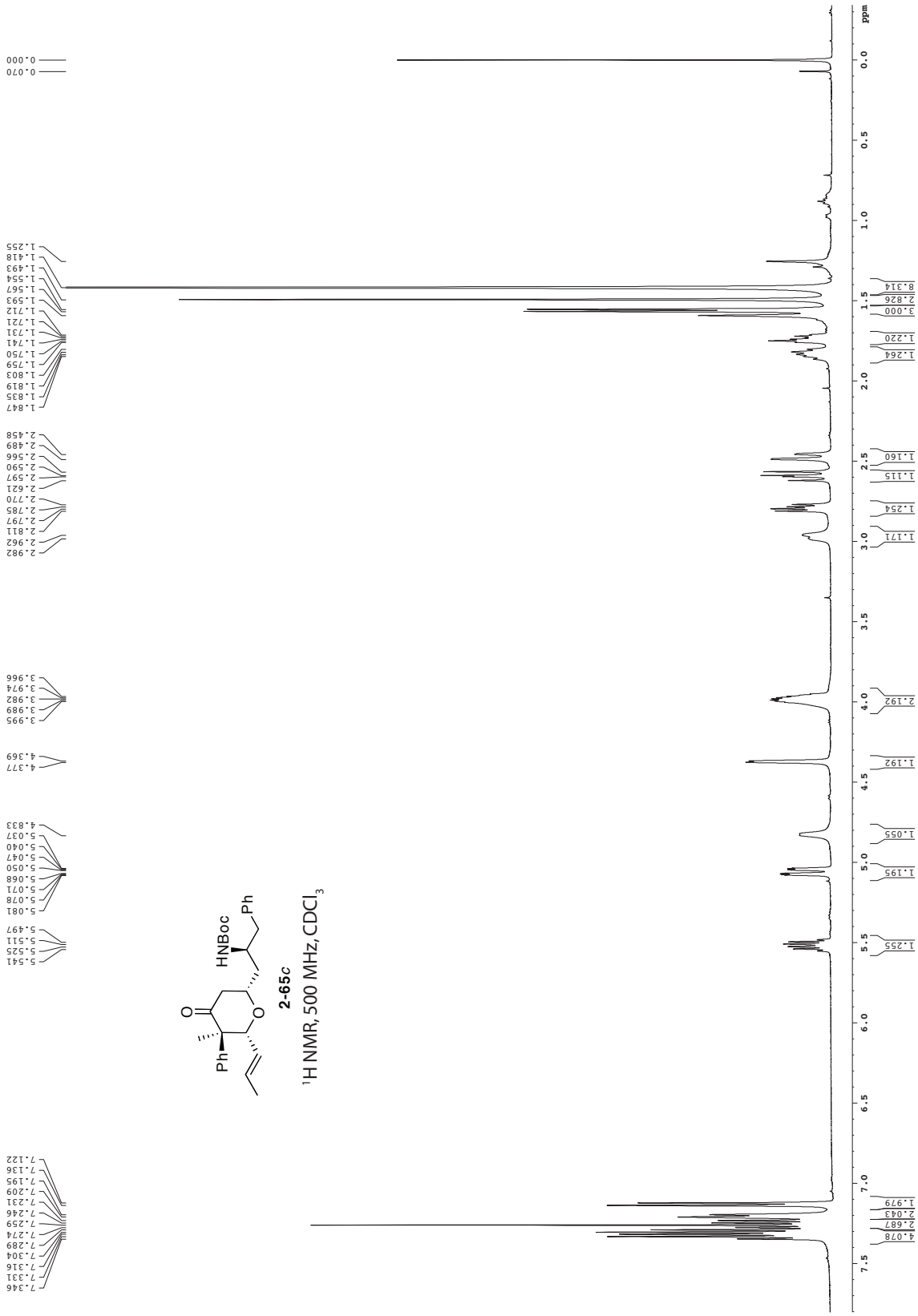
E(scf) = –737.691123 au

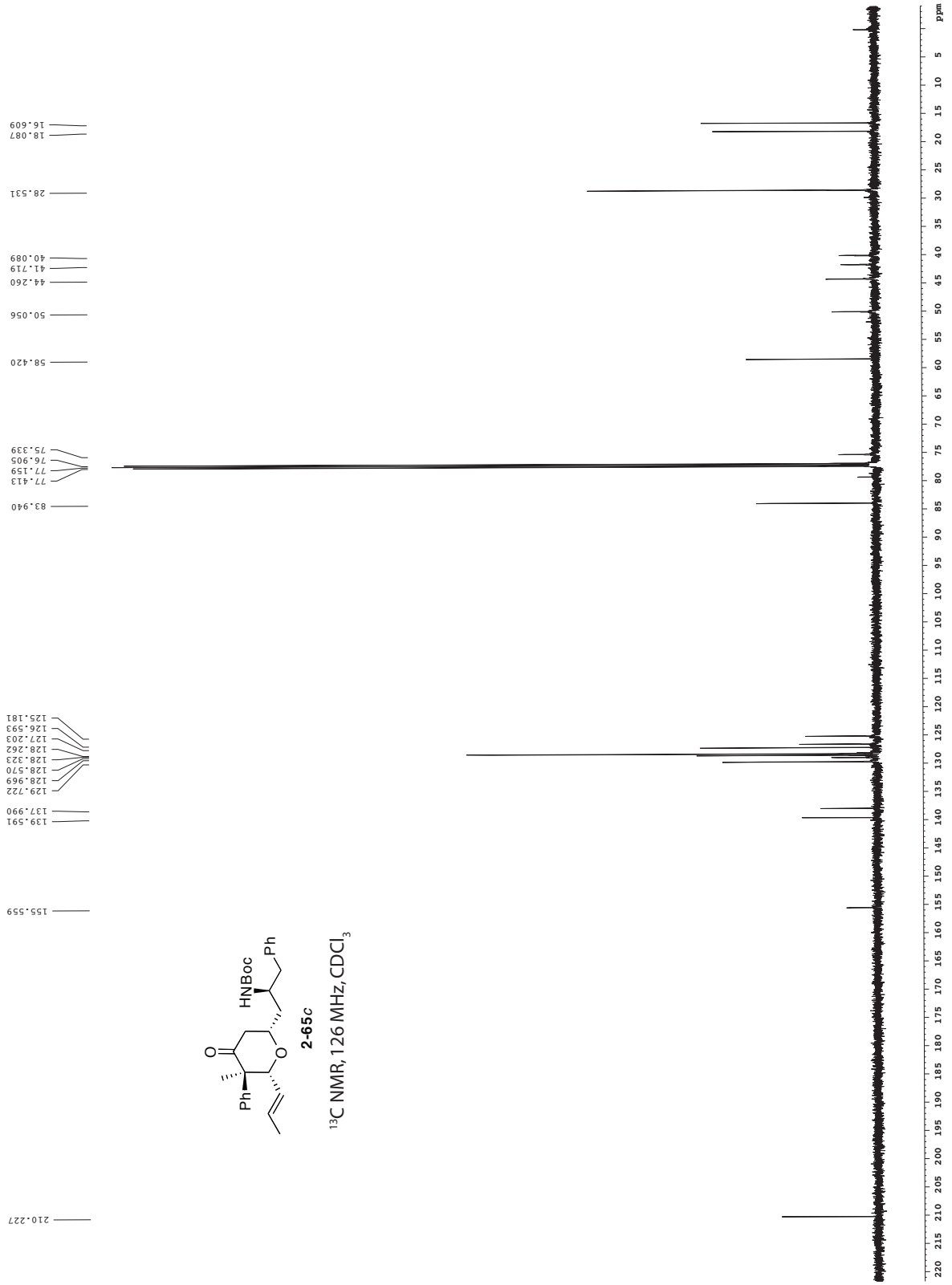

BocNH
O
OTBS
Ph
Ph
2-118
^{1}H NMR, 500 MHz, CDCl$_3$

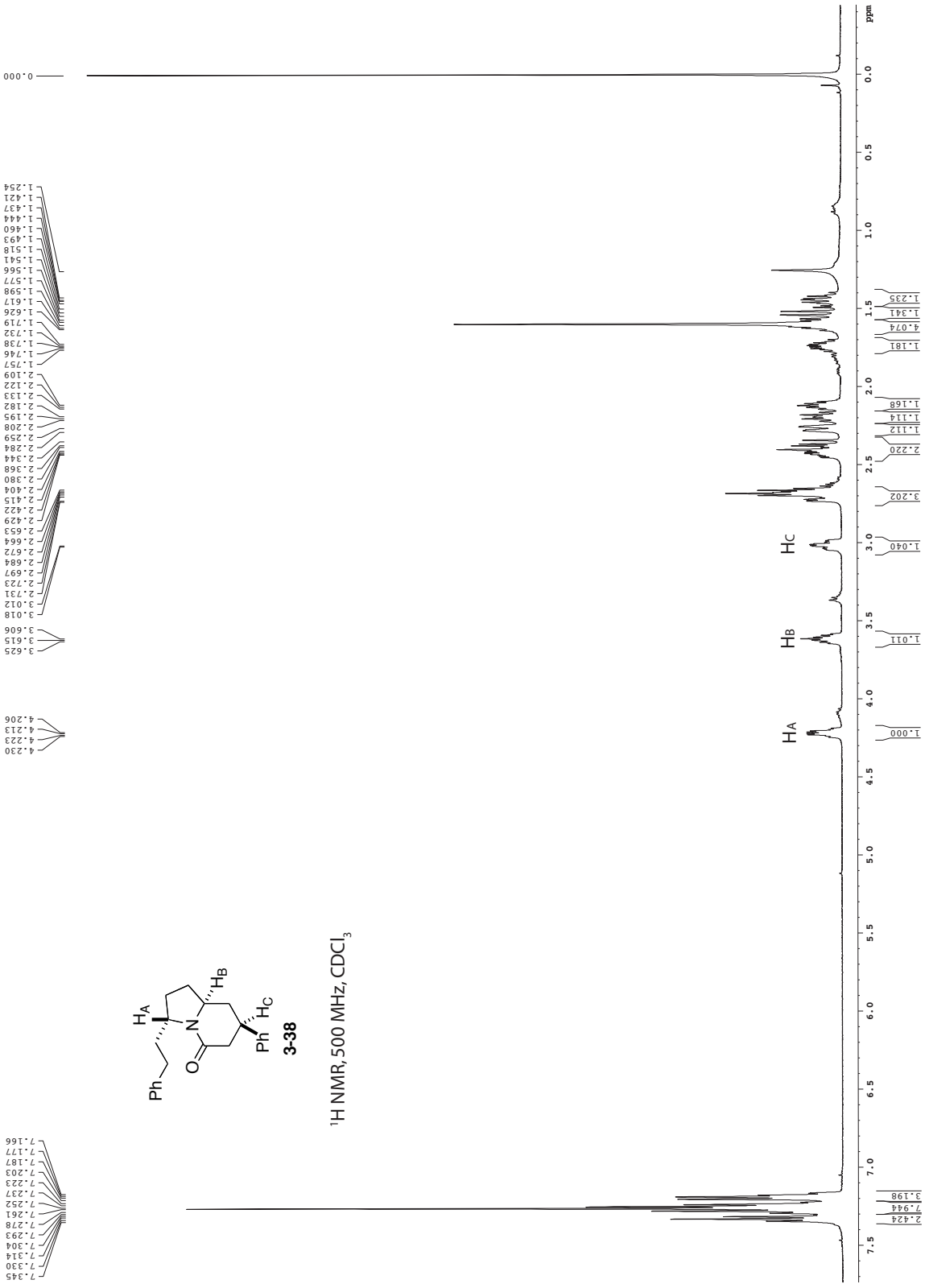

17.966
19.596
25.682
28.438
40.406
43.500
48.618
49.059
76.905
77.159
77.414
79.274
118.958
126.277
126.585
126.641
127.885
128.612
129.098
129.152
129.423
129.490
138.291
139.952
141.357
155.369
BocNH
O
OTBS
Ph
Ph
2-118
^{13}C NMR, 126 MHz, CDCl$_3$
ppm

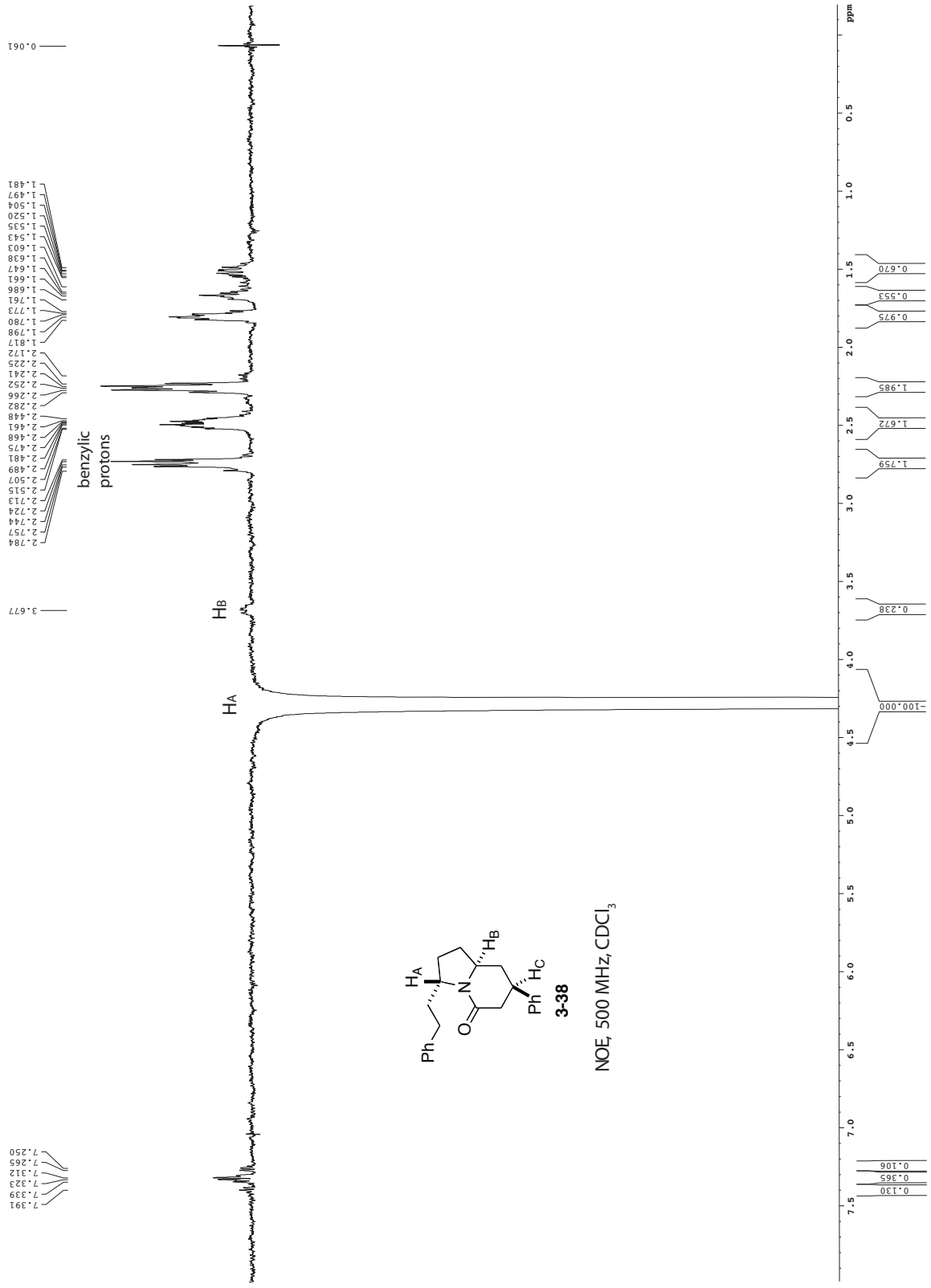

BocNH
O
OTBS
Ph
Ph
2-118
^{1}H NMR, 500 MHz, $CDCl_3$

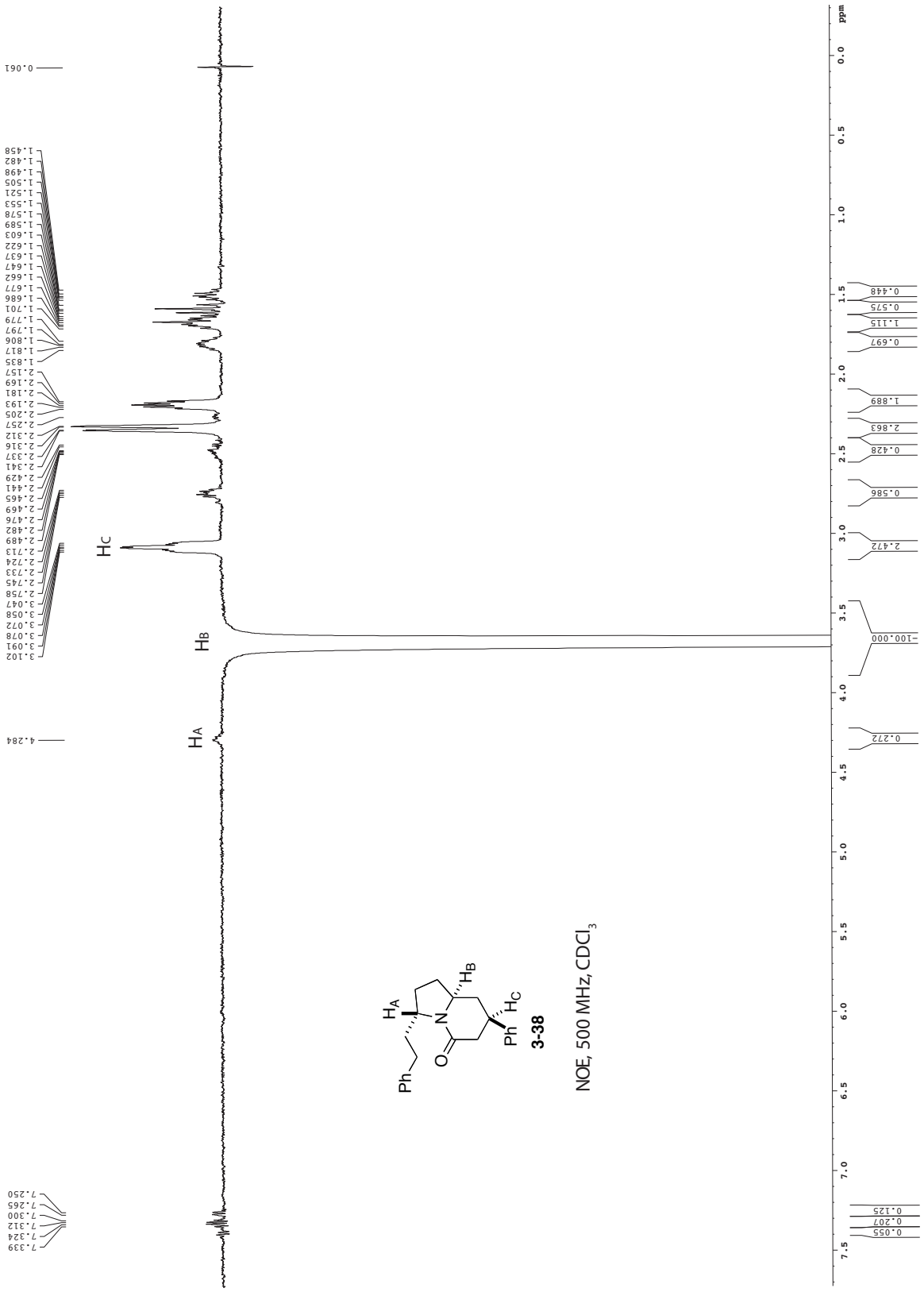

BocNH
O
OTBS
Ph
Ph
2-118
^{13}C NMR, 126 MHz, $CDCl_3$
155.369
141.357
139.952
138.291
129.490
129.423
129.152
129.098
128.612
127.885
126.641
126.585
126.277
118.958
79.274
77.414
77.159
76.905
49.059
48.618
43.500
40.406
28.438
25.682
19.596
17.966
ppm

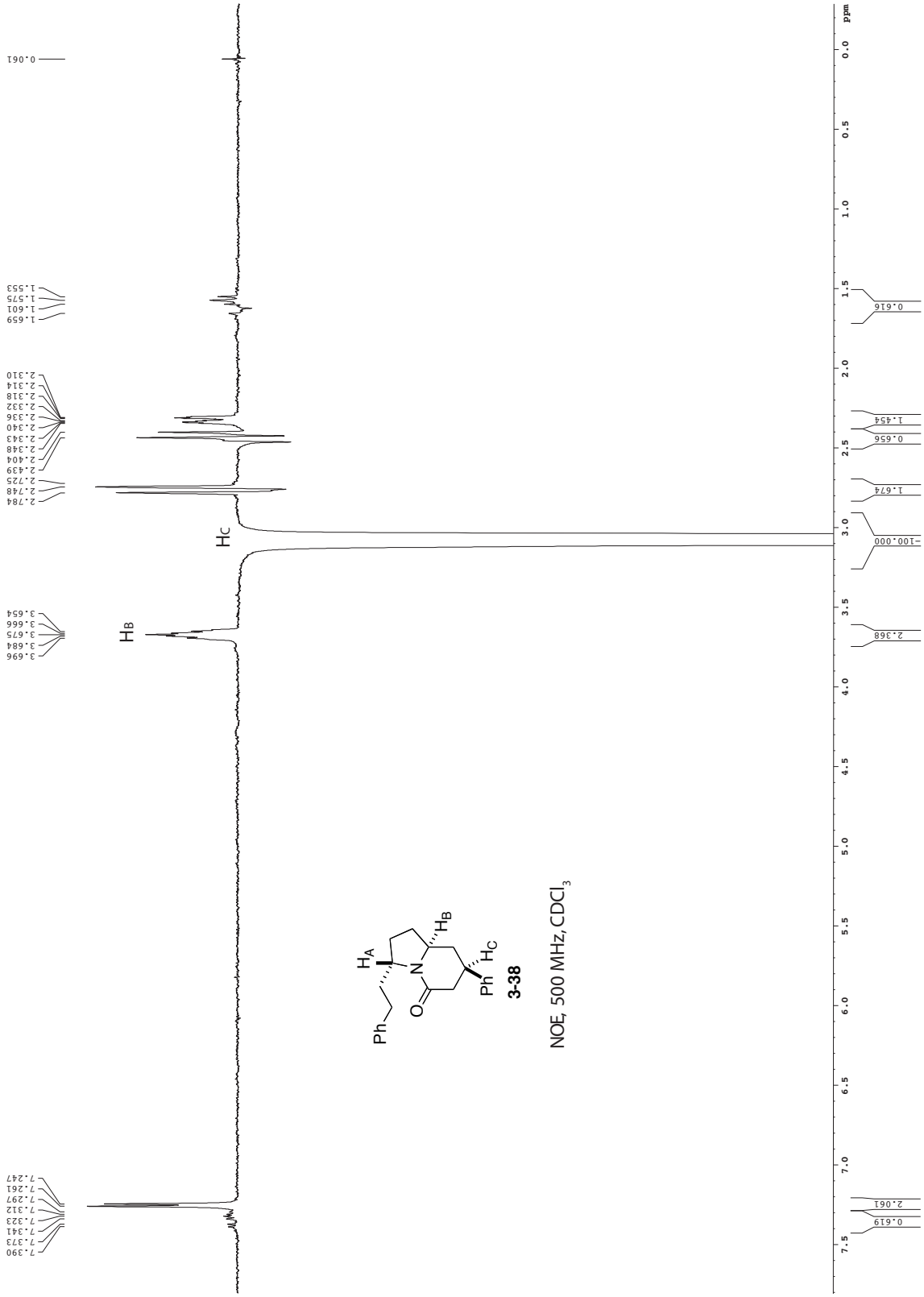

HNBoc
Ph
Ph
O
O
2-65c
^{1}H NMR, 500 MHz, CDCl$_3$
ppm

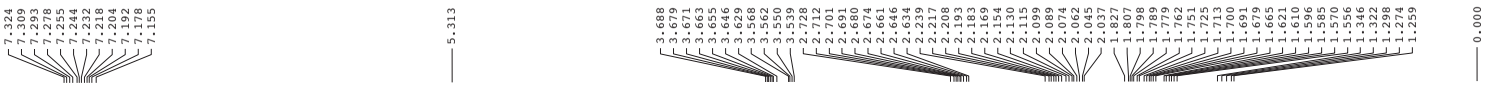

HNBoc
Ph
O
O
Ph
2-65c
^{13}C NMR, 126 MHz, $CDCl_3$
210.227
155.559
139.591
137.990
129.722
128.969
128.570
128.323
128.262
127.203
126.593
125.181
83.940
77.413
77.159
76.905
75.339
58.420
50.056
44.260
41.719
40.089
28.531
18.087
16.609
ppm

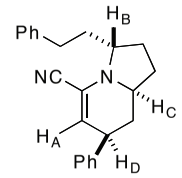

Ph
HA
N
O
HB
Ph
HC
3-38
1H NMR, 500 MHz, CDCl3
HA
HB
HC
ppm


benzylic protons
H_A
H_B
Ph
N
O
H_A
H_B
Ph
H_C
3-38
NOE, 500 MHz, $CDCl_3$
ppm


HA
HB
HC
Ph
N
O
Ph
HA
HB
HC
3-38
NOE, 500 MHz, CDCl3

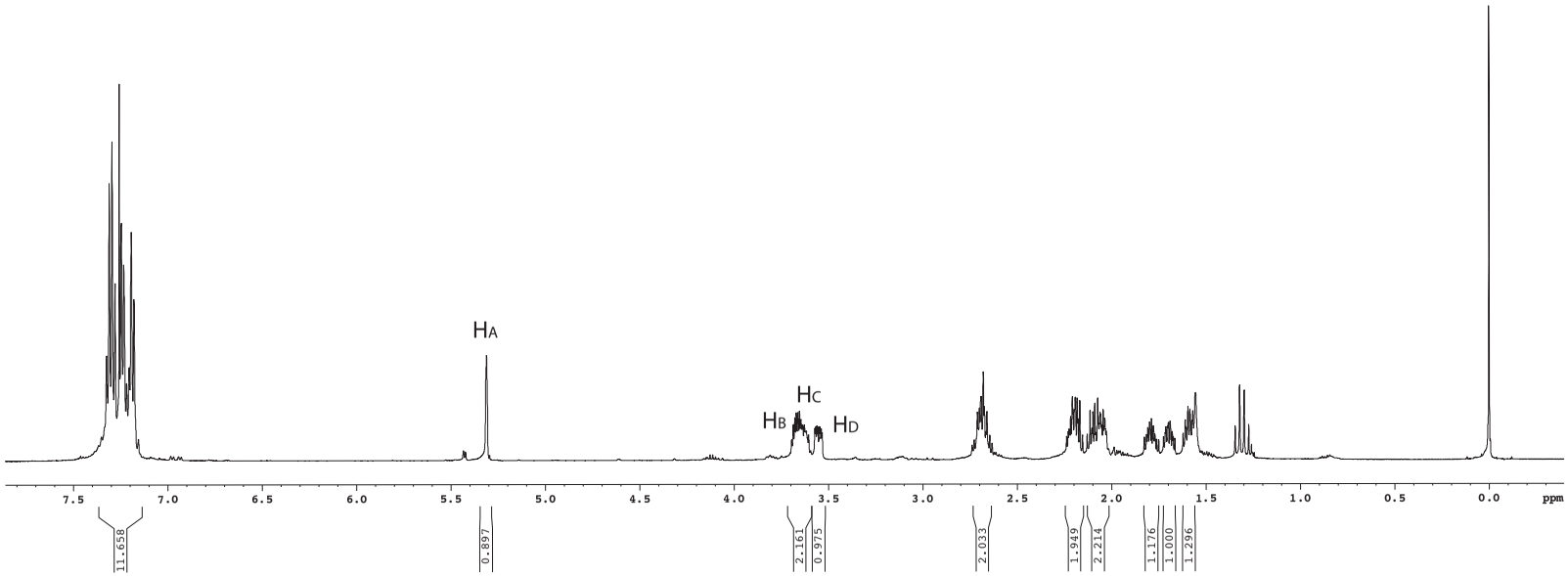

0.061
1.553
1.575
1.601
1.659
2.310
2.314
2.318
2.332
2.336
2.340
2.343
2.348
2.404
2.439
2.725
2.748
2.784
3.654
3.666
3.675
3.684
3.696
7.247
7.261
7.297
7.312
7.323
7.341
7.373
7.390
HC
HB
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
0.616
1.454
0.656
1.674
100.000
2.368
2.061
0.619
HA
HB
HC
Ph
Ph
O
N
3-38
NOE, 500 MHz, CDCl3

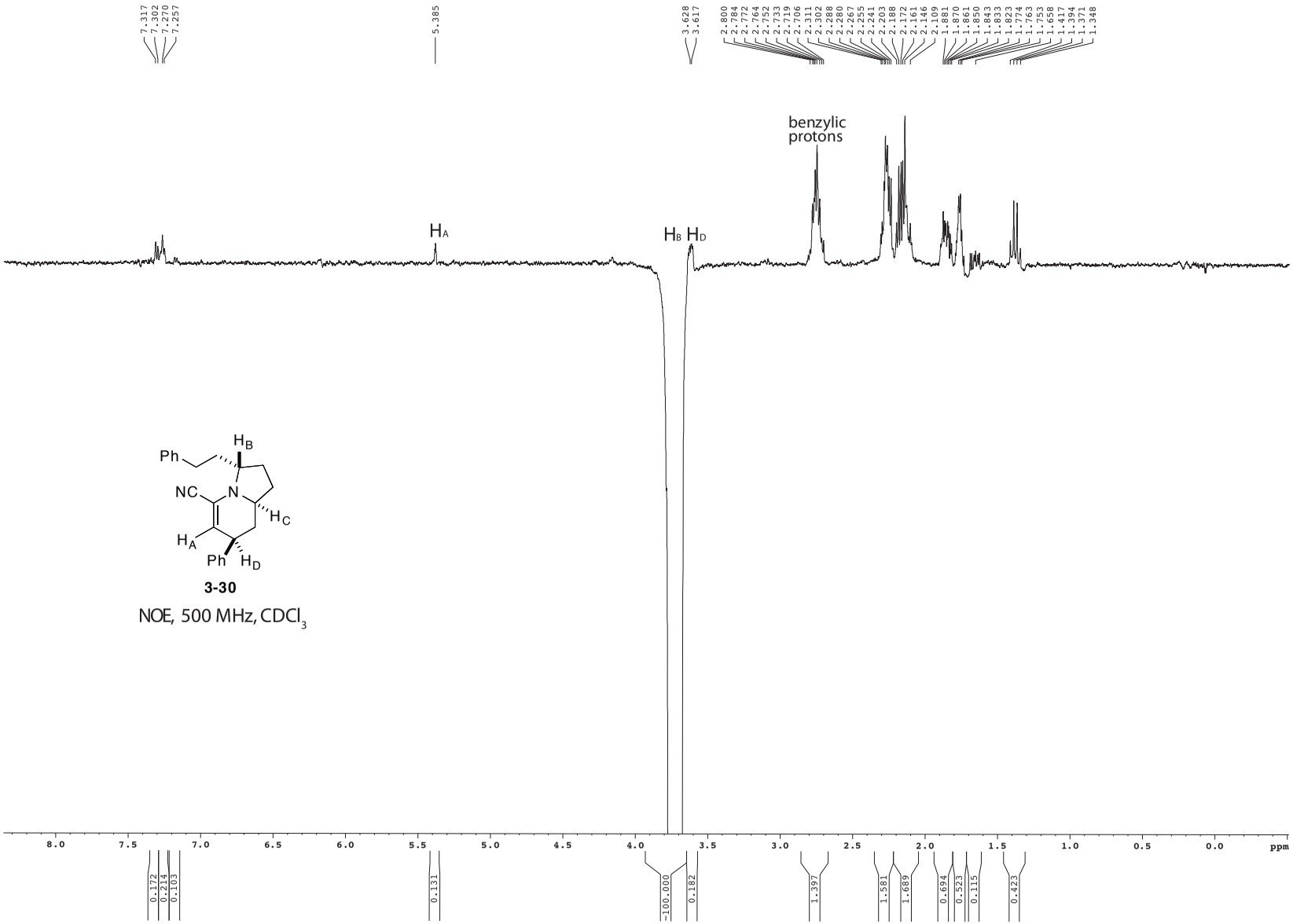




3-30

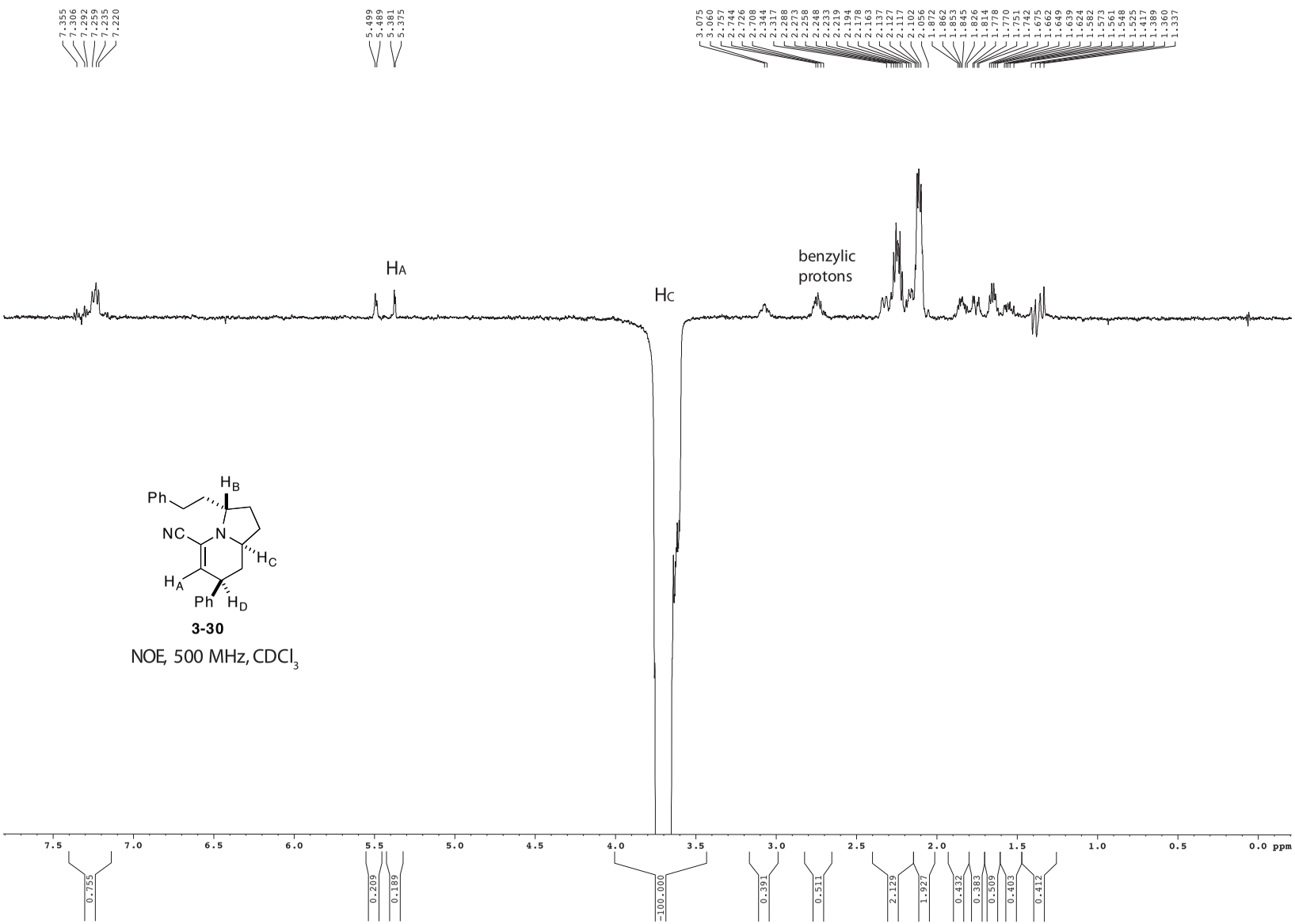
^{1}H NMR, 500 MHz, $CDCl_3$



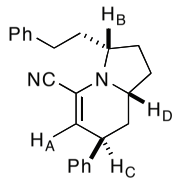


3-30

NOE, 500 MHz, $CDCl_3$

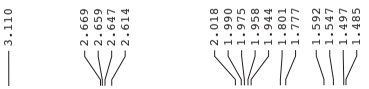

7.355
7.306
7.292
7.259
7.235
7.220
5.499
5.489
5.381
5.375
3.075
3.060
2.757
2.744
2.726
2.708
2.344
2.317
2.288
2.273
2.258
2.248
2.233
2.219
2.194
2.178
2.163
2.137
2.127
2.117
2.102
2.055
1.872
1.862
1.853
1.845
1.826
1.814
1.778
1.770
1.751
1.742
1.675
1.662
1.649
1.639
1.624
1.582
1.573
1.561
1.548
1.525
1.417
1.389
1.360
1.337
HA
HC
benzylic
protons
HB
Ph
NC
N
HC
HA
Ph
HD
3-30
NOE, 500 MHz, CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
0.755
0.209
0.189
-100.000
0.391
0.511
2.129
1.927
0.432
0.383
0.509
0.403
0.412

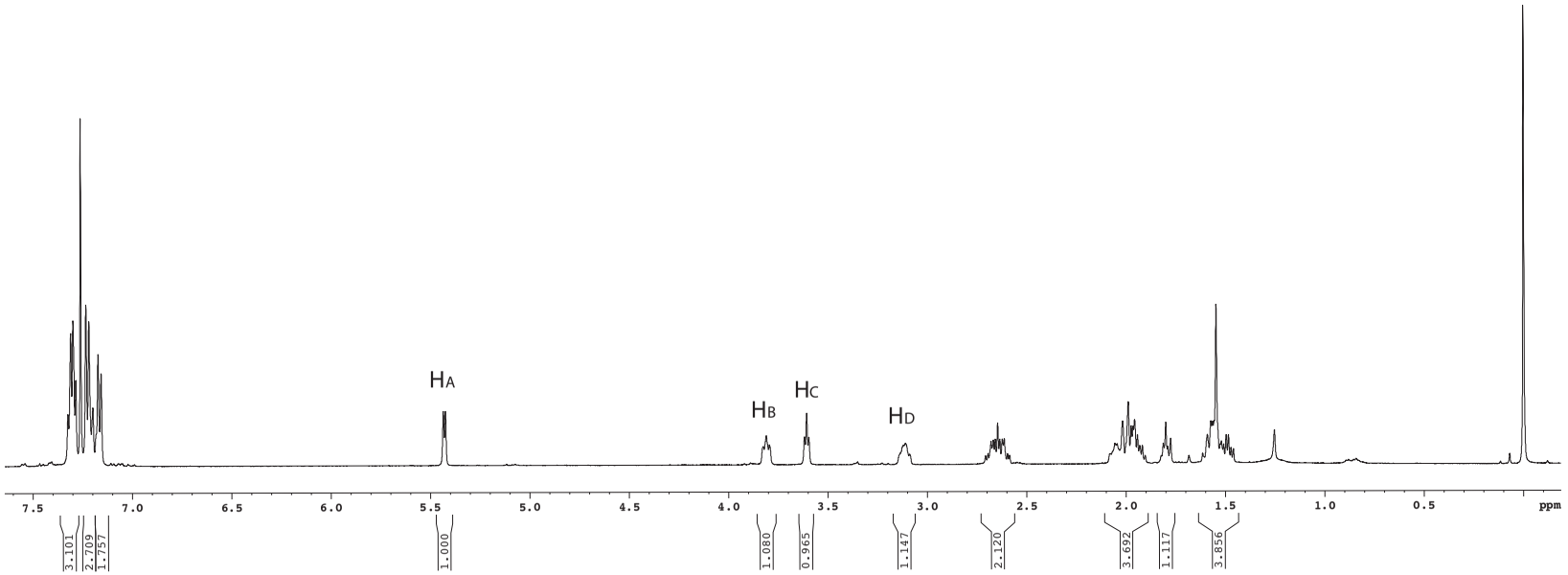
7.374
7.358
7.312
7.257
7.243
5.379
5.371
2.127
2.119
2.101
1.387
1.363
1.339
HA
HD
2.561
0.949
1.599
0.470
100.000
0.0 ppm
HB
HC
HD
Ph
N
NC
HA
Ph
3-30
NOE, 500 MHz, CDCl3

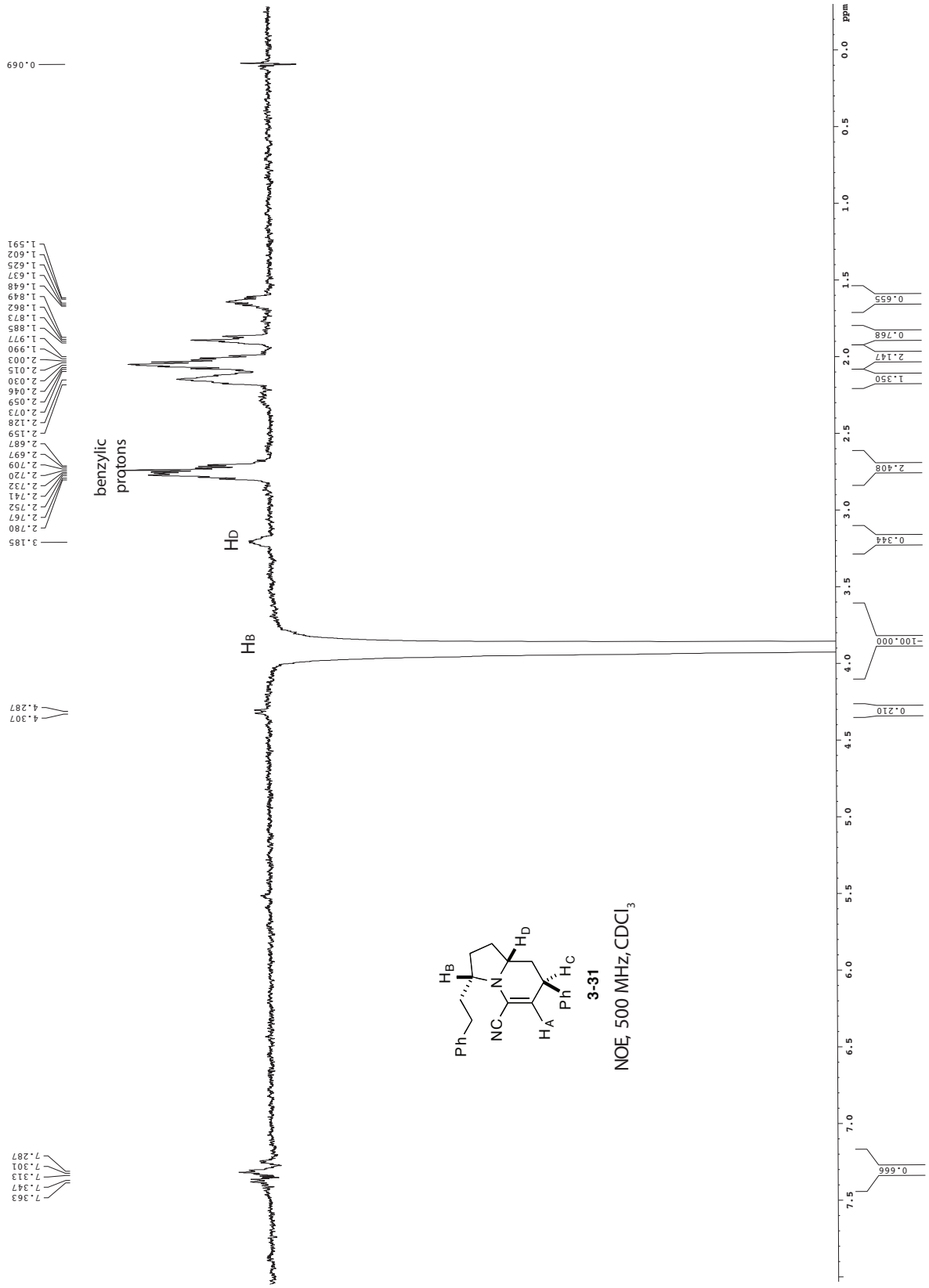


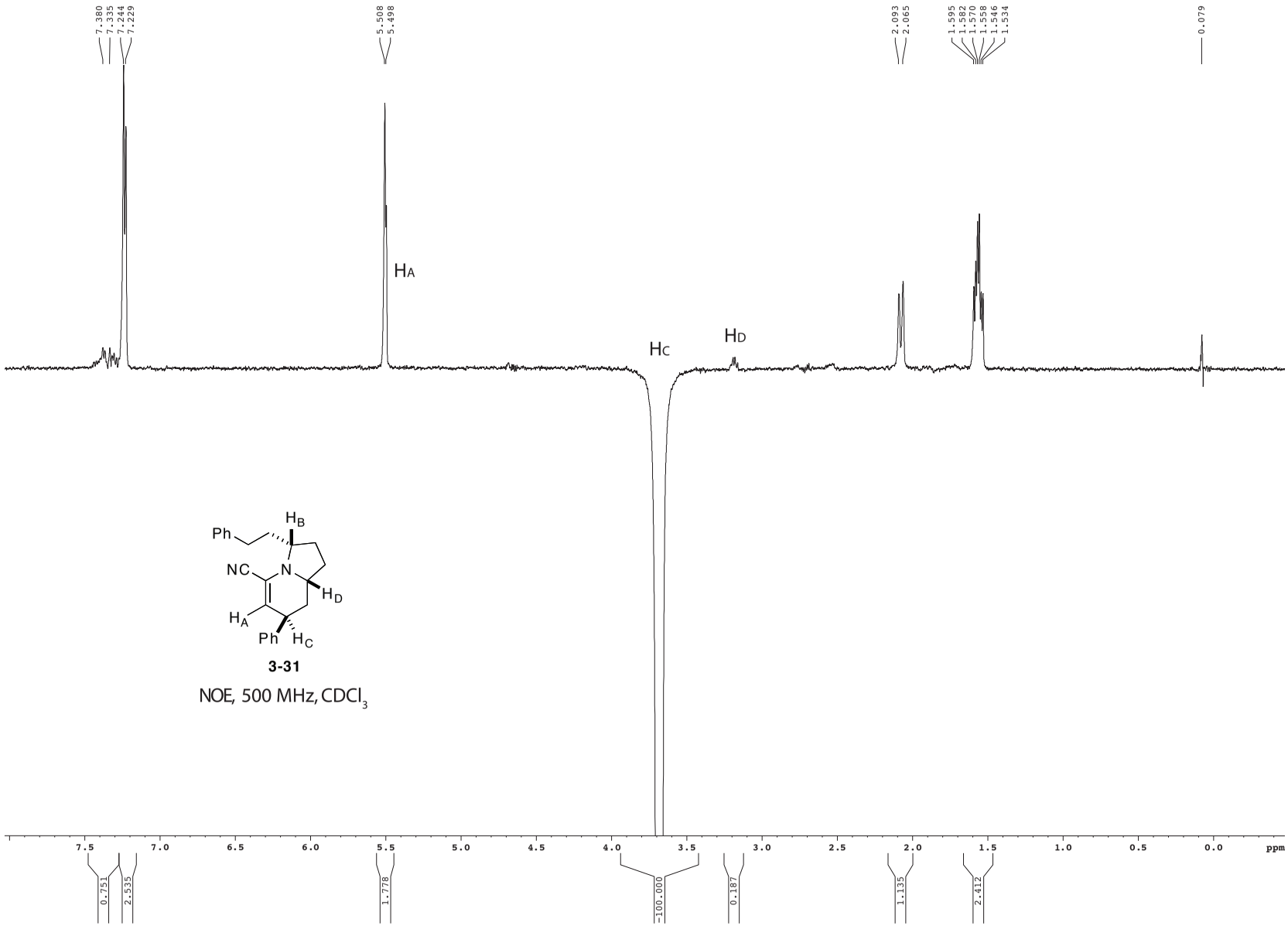
3-31

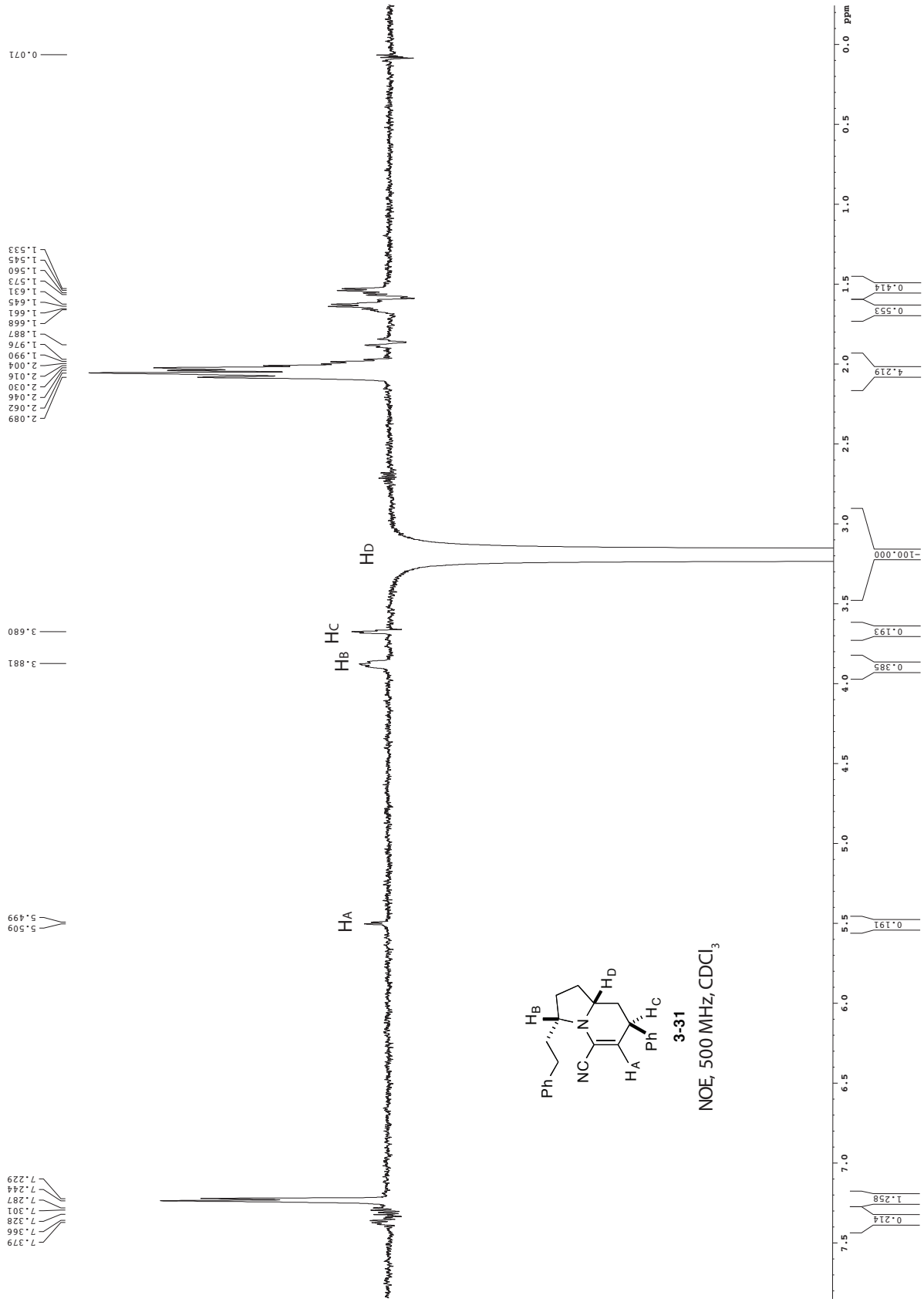
^{1}H NMR, 500 MHz, $CDCl_3$

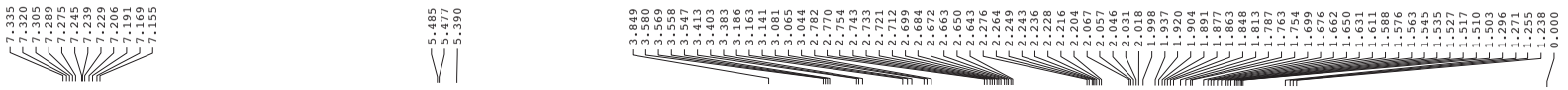


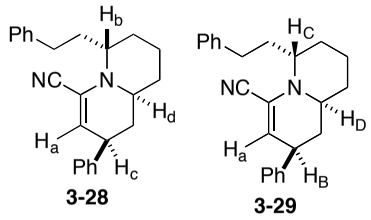



benzylic protons
H_D
H_B
H_B
H_D
Ph
NC
N
H_A
Ph
H_C
3-31
NOE, 500 MHz, $CDCl_3$


7.380
7.335
7.244
7.229
5.508
5.498
2.093
2.065
1.595
1.582
1.570
1.558
1.546
1.534
0.079
HA
HC
HD
Ph
HB
NC
N
HD
HA
Ph
HC
3-31
NOE, 500 MHz, CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.751
2.535
1.778
100.000
0.187
1.135
2.412

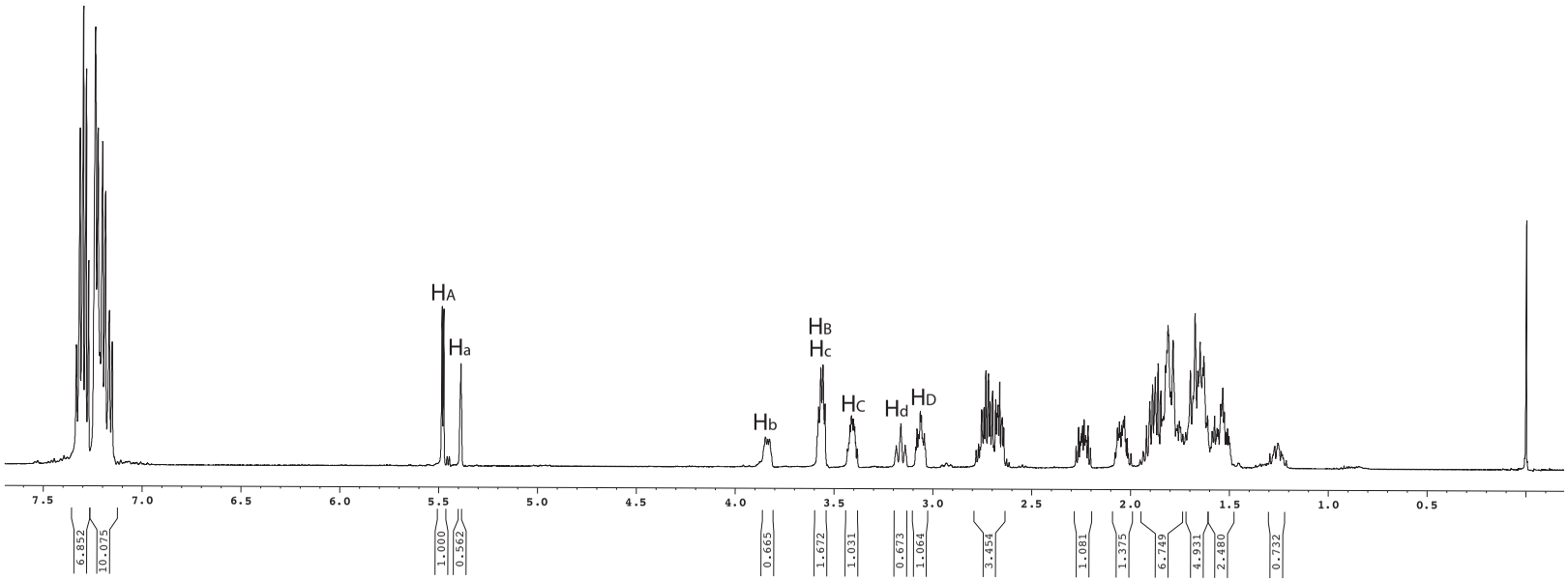

NOE, 500 MHz, CDCl3
3-31
HA
HB
HC
HD
Ph
NC
N
Ph
7.379
7.366
7.328
7.301
7.287
7.244
7.229
5.509
5.499
3.680
3.881
2.089
2.062
2.046
2.030
2.016
2.004
1.990
1.976
1.887
1.668
1.661
1.645
1.631
1.573
1.560
1.545
1.533
0.071
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
0.214
1.258
0.191
0.385
0.193
100.000
0.553
0.414
4.219

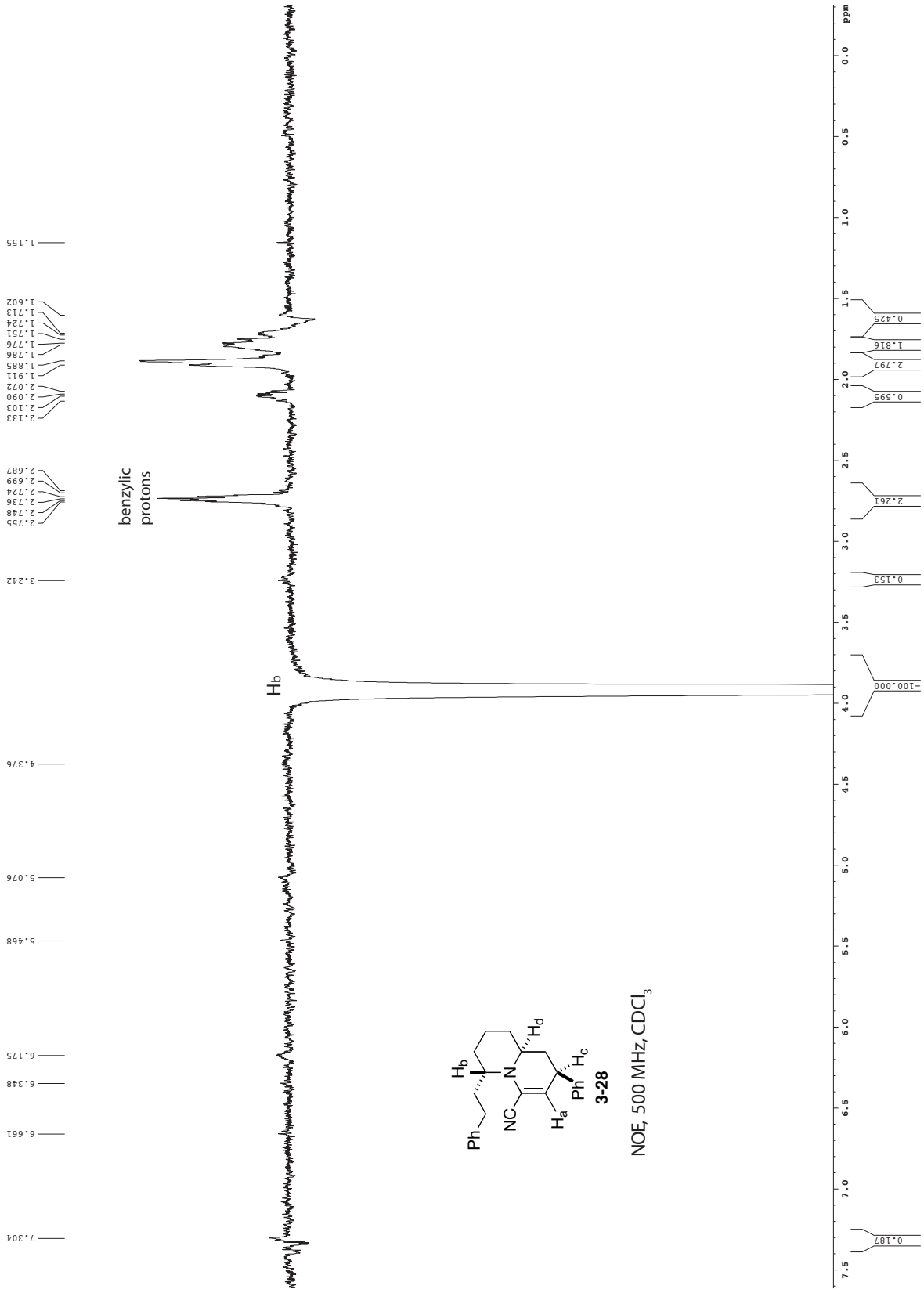


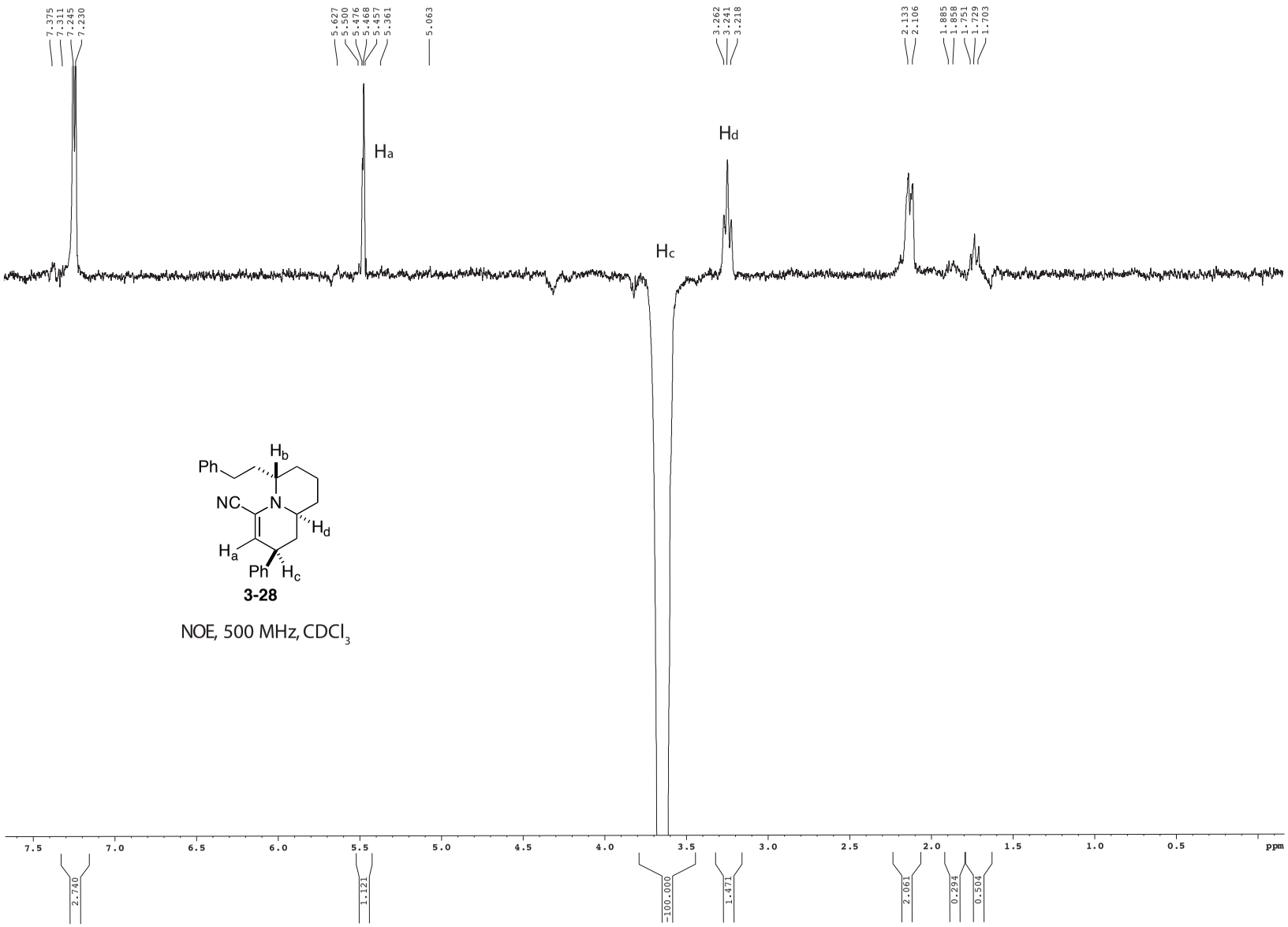


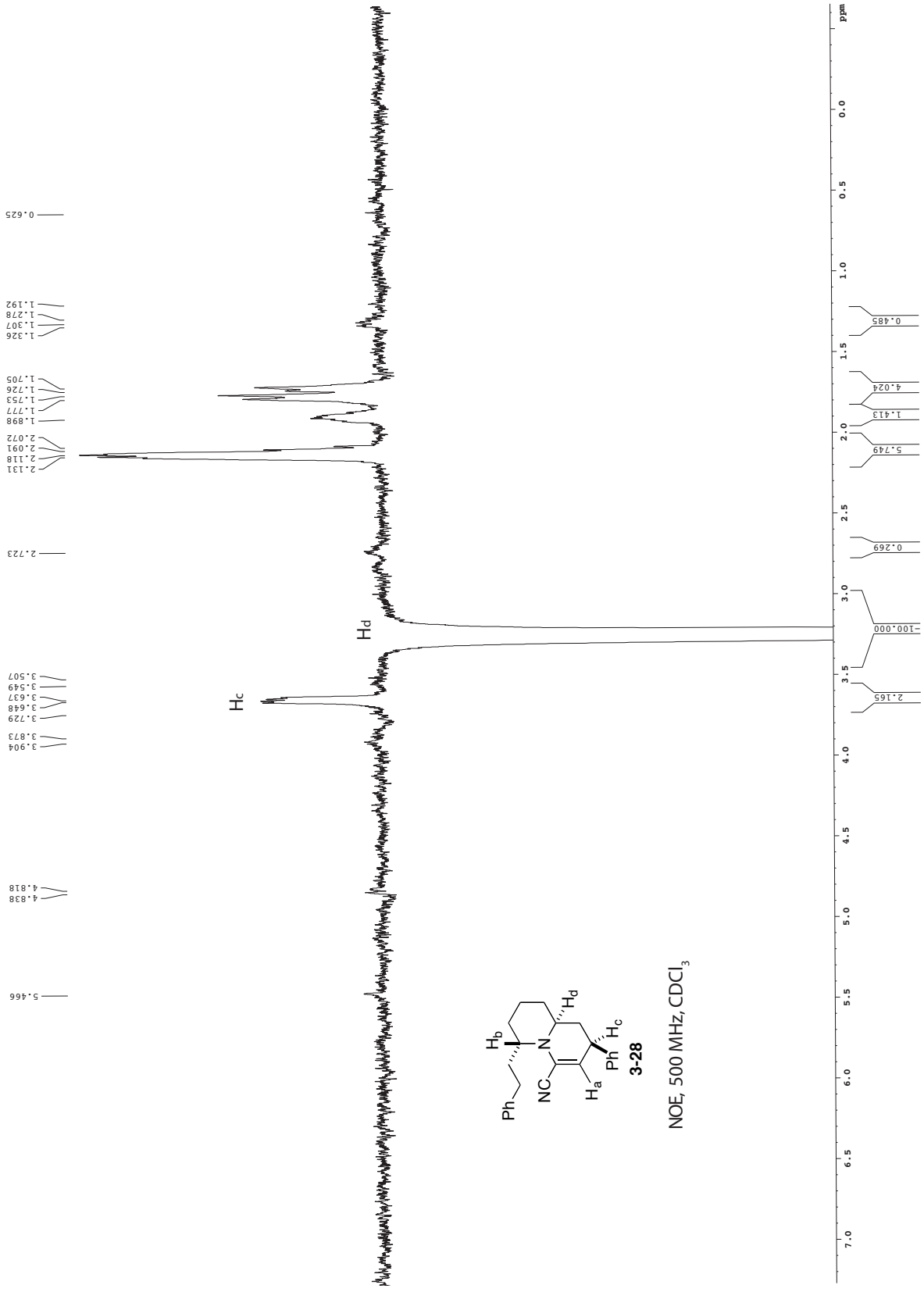
3-28 **3-29**

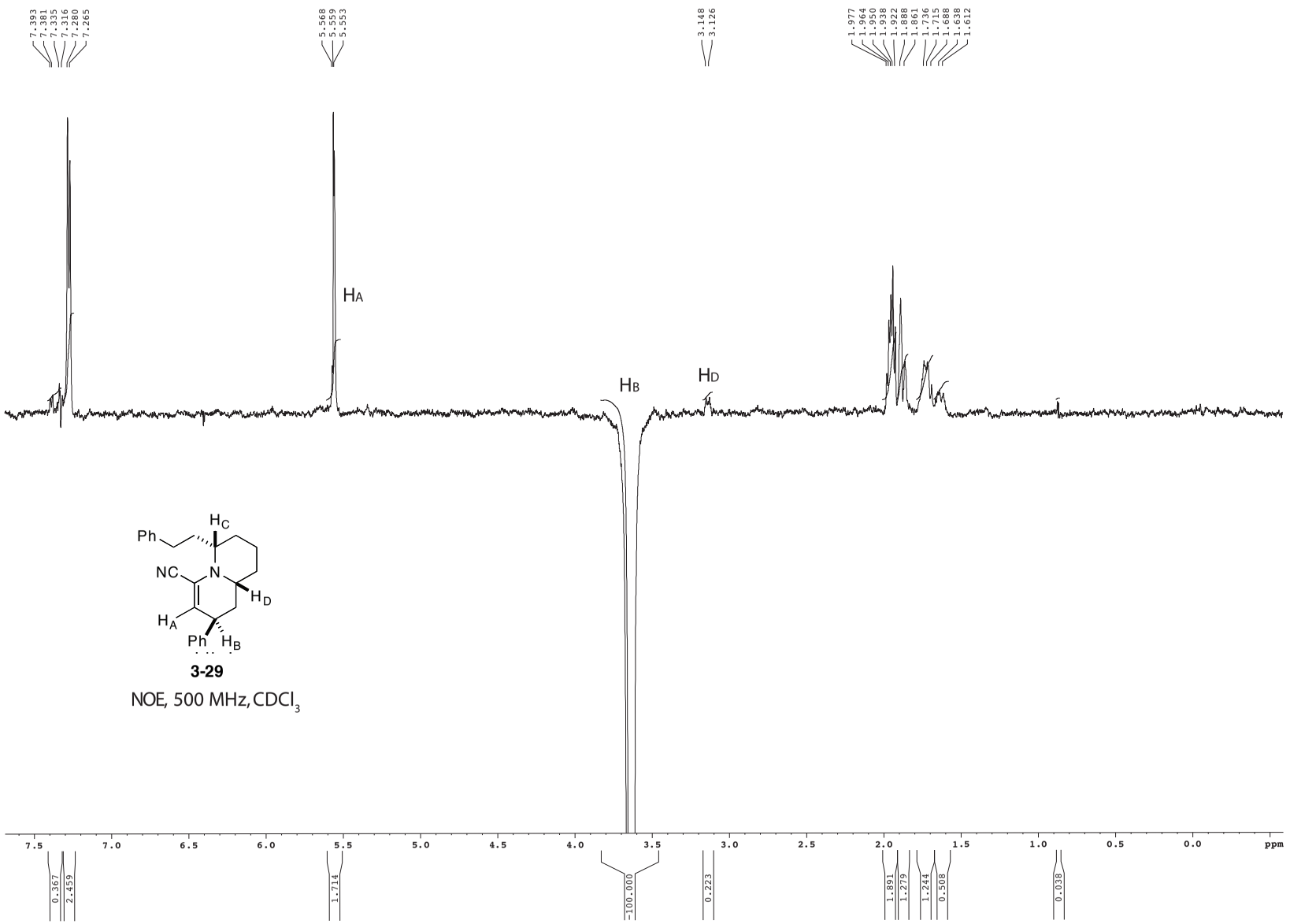
^{1}H NMR, 500 MHz, $CDCl_3$

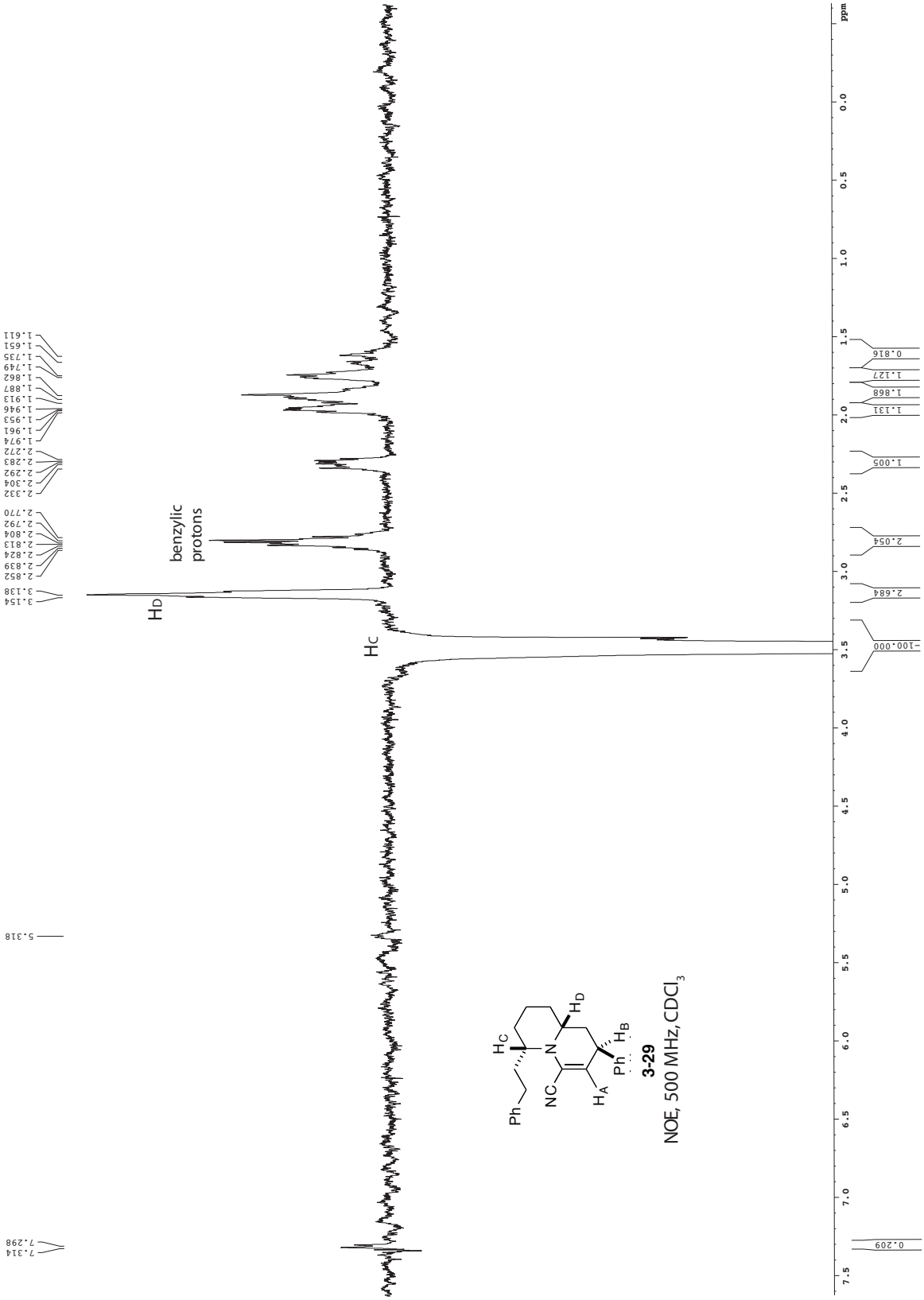


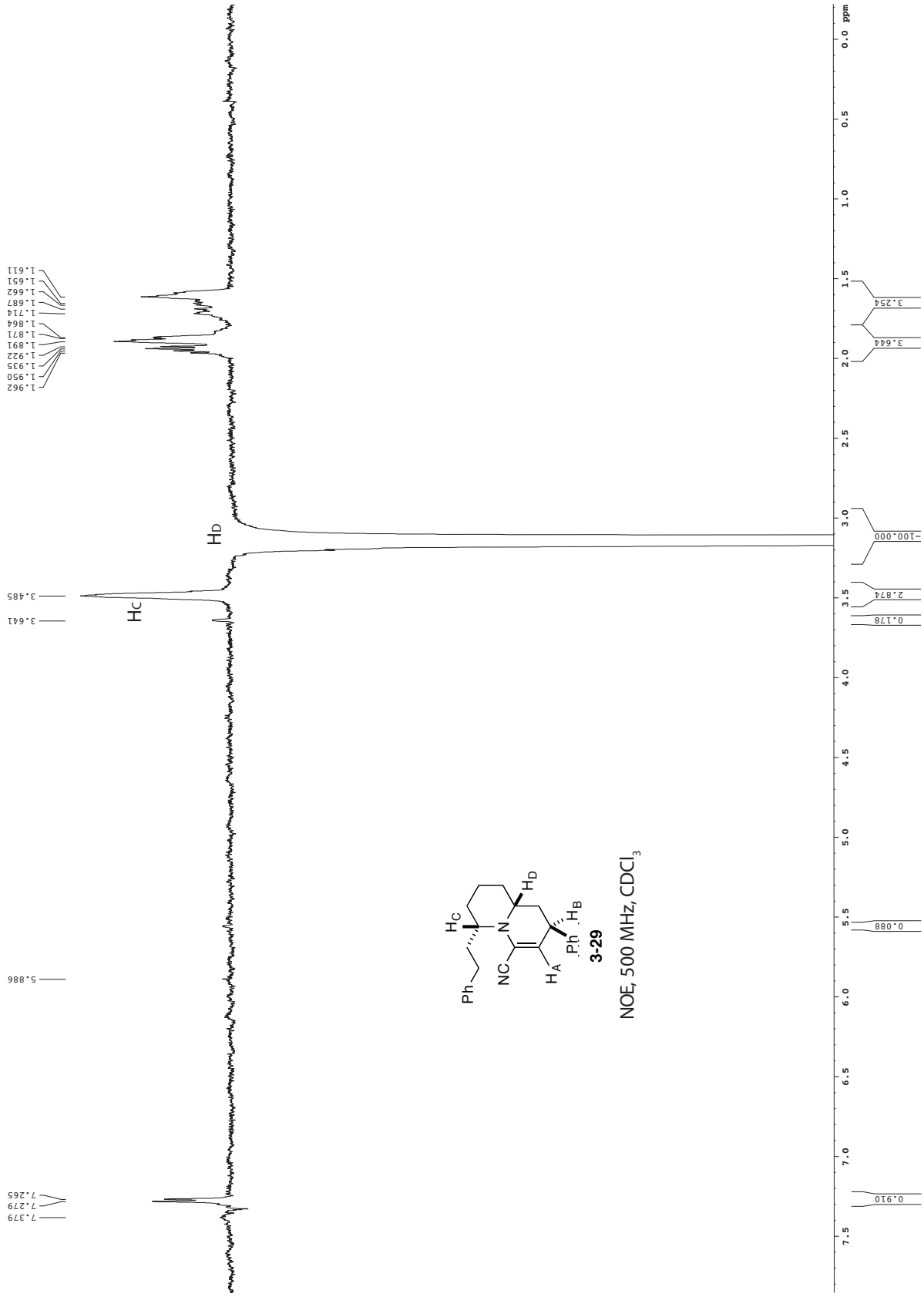

benzylic
protons
Hb
Ph
NC
Ha
Hb
Hd
Ph
Hc
3-28
NOE, 500 MHz, CDCl3
ppm

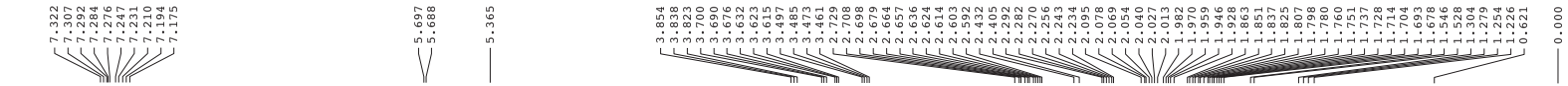

7.375
7.311
7.245
7.230
5.627
5.500
5.476
5.468
5.457
5.361
5.063
3.262
3.241
3.218
2.133
2.106
1.885
1.858
1.751
1.729
1.703
Ha
Hc
Hd
Hb
Ph
NC
N
Hd
Ha
Ph
Hc
3-28
NOE, 500 MHz, CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.740
1.121
-100.000
1.471
2.061
0.294
0.504

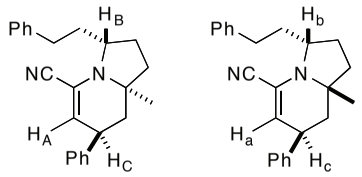

Hc
Hd
Hb
Ha
Hd
Hc
Ph
NC
N
Ph
3-28
NOE, 500 MHz, CDCl3
ppm


7.393
7.381
7.335
7.316
7.280
7.265
5.568
5.559
5.553
3.148
3.126
1.977
1.964
1.950
1.938
1.922
1.888
1.861
1.736
1.715
1.688
1.638
1.612
HA
HB
HD
Ph
HC
NC
N
HD
HA
Ph
HB
3-29
NOE, 500 MHz, CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.367
2.459
1.714
100.000
0.223
1.891
1.279
1.244
0.508
0.038


benzylic protons
H_D
H_C
Ph
NC
N
H_C
H_D
H_A
Ph
H_B
3-29
NOE, 500 MHz, $CDCl_3$

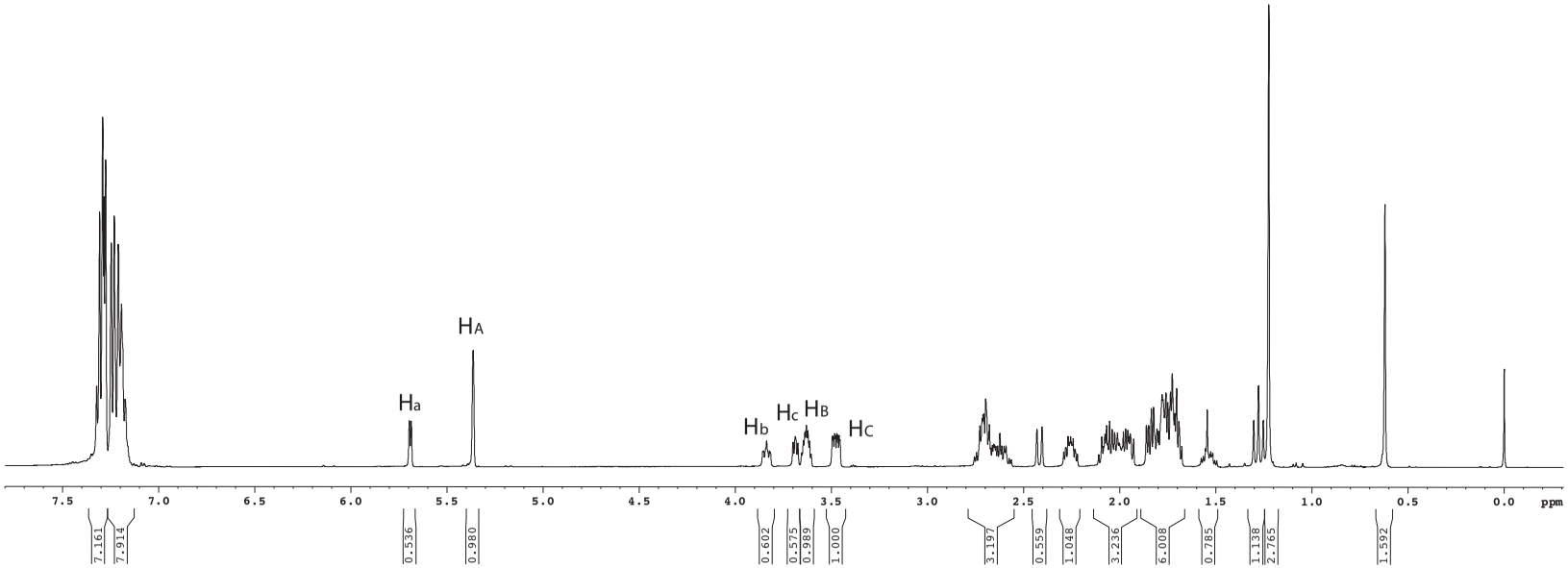

HD
HC
HC
HD
NC
N
Ph
HA
HB
Ph
3-29
NOE, 500 MHz, CDCl3

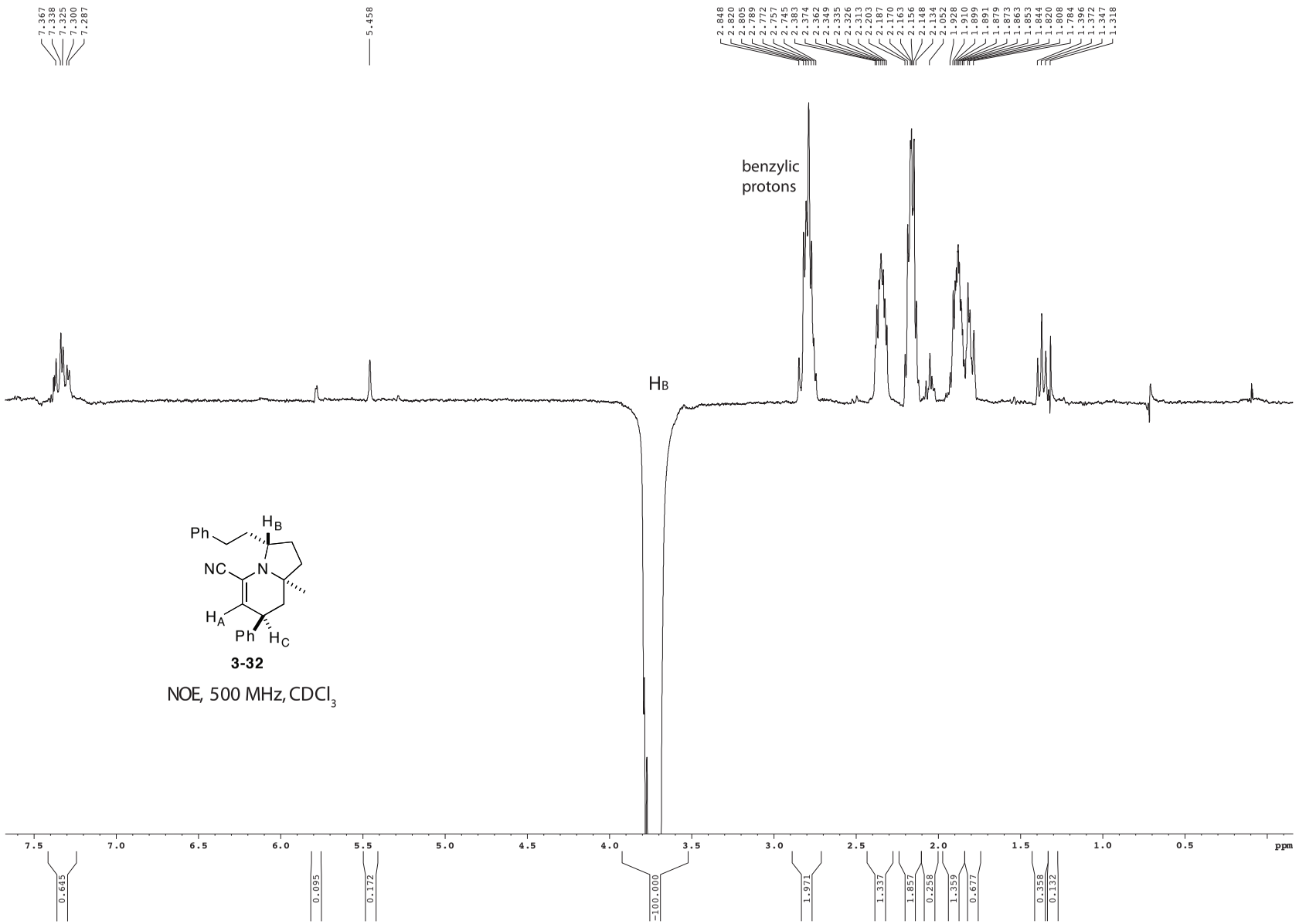


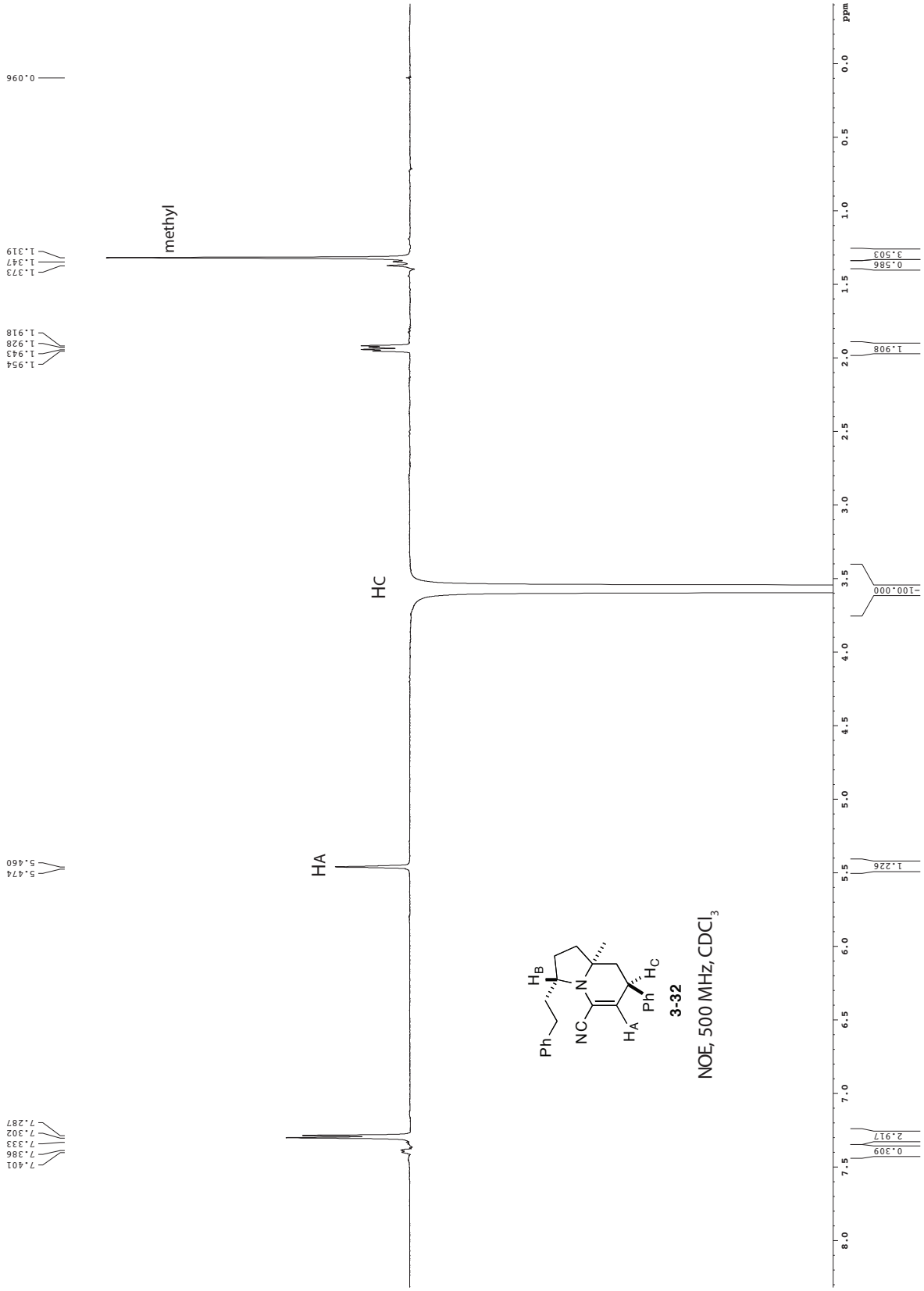


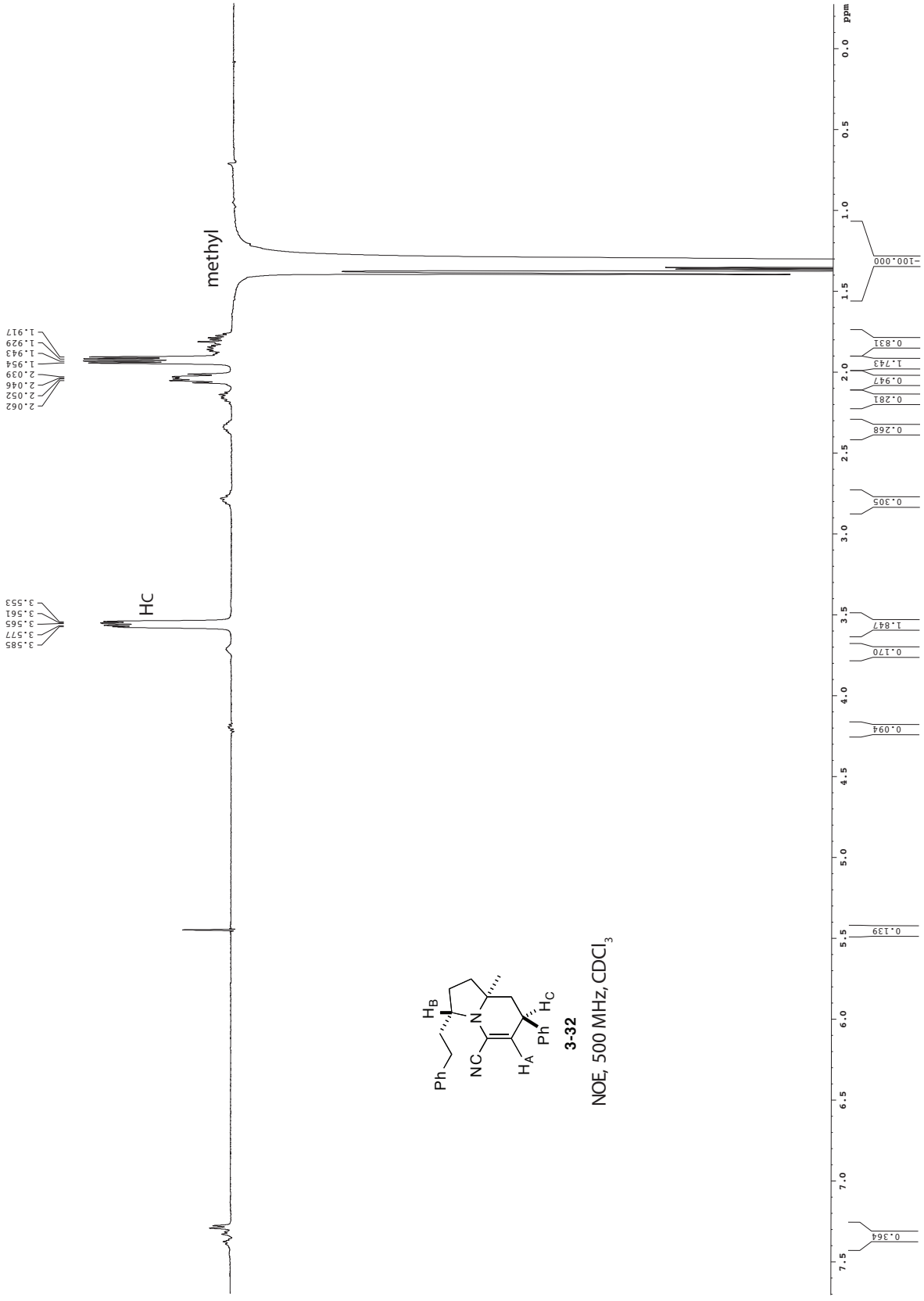
3-32 **3-33**

^{1}H NMR, 500 MHz, $CDCl_3$



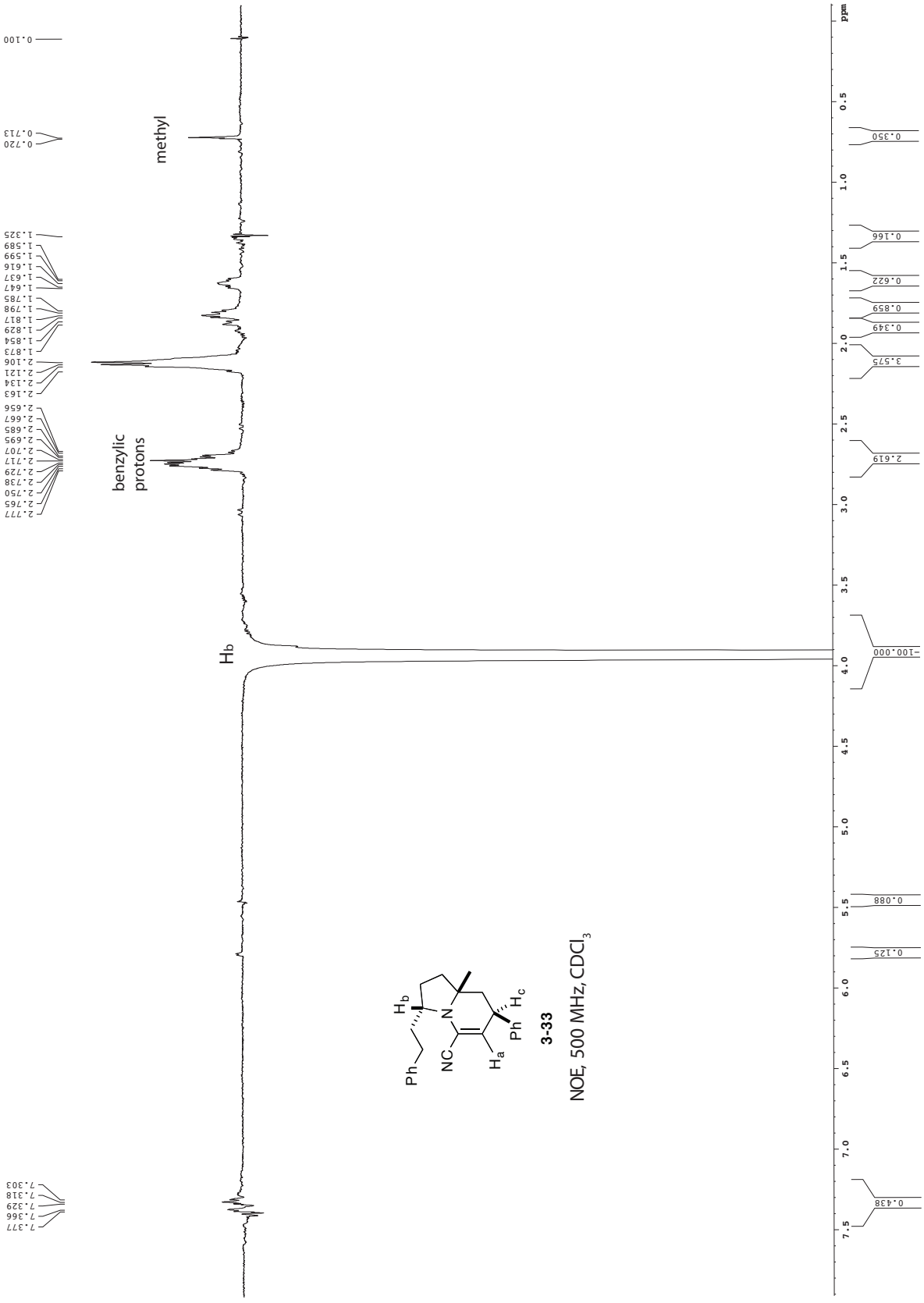

benzylic protons
HB
Ph
HB
NC
N
HA
Ph
HC
3-32
NOE, 500 MHz, CDCl3
ppm

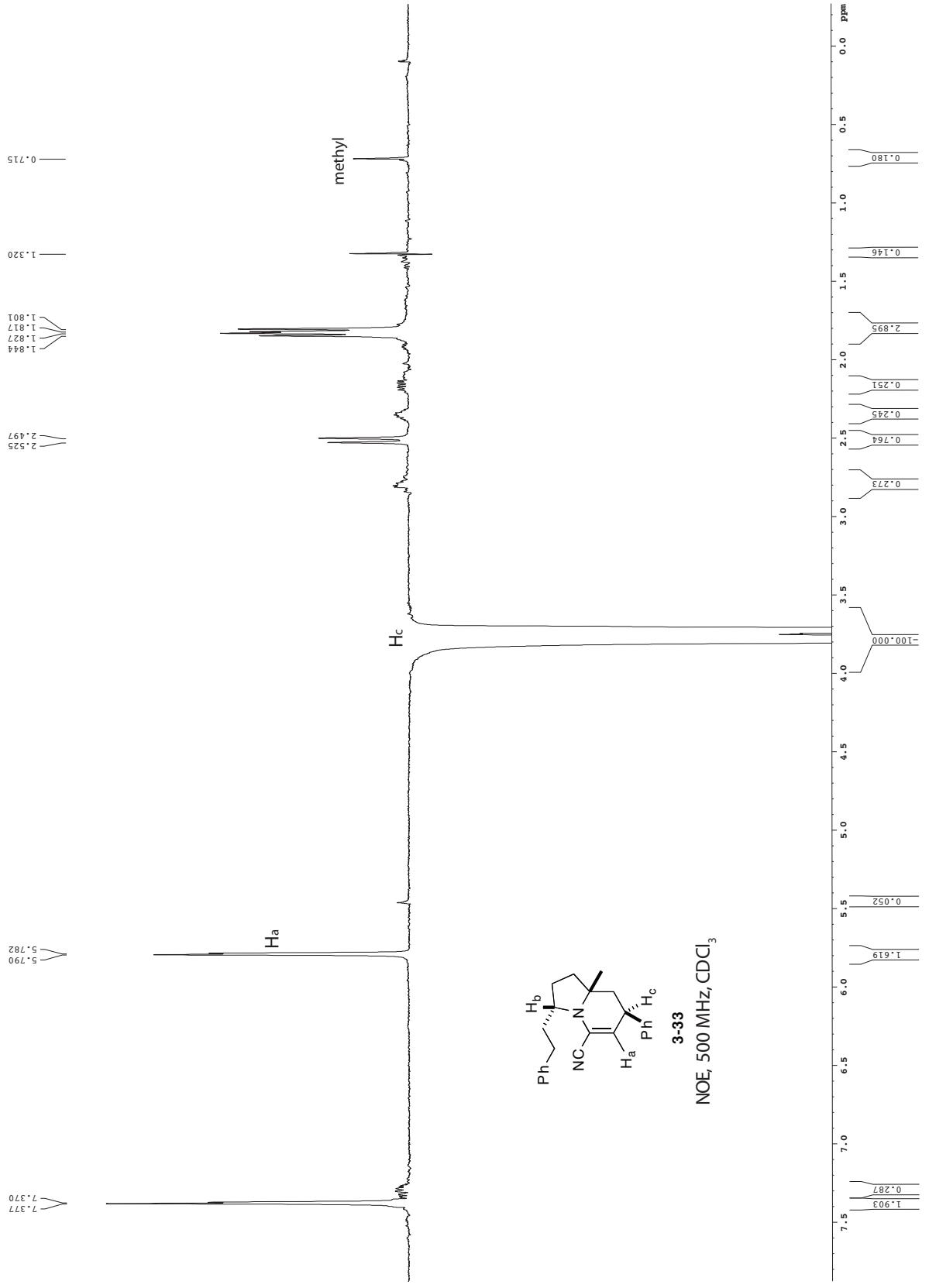

methyl
HA
HC
Ph
NC
HA
Ph
HC
HB
3-32
NOE, 500 MHz, CDCl3
ppm

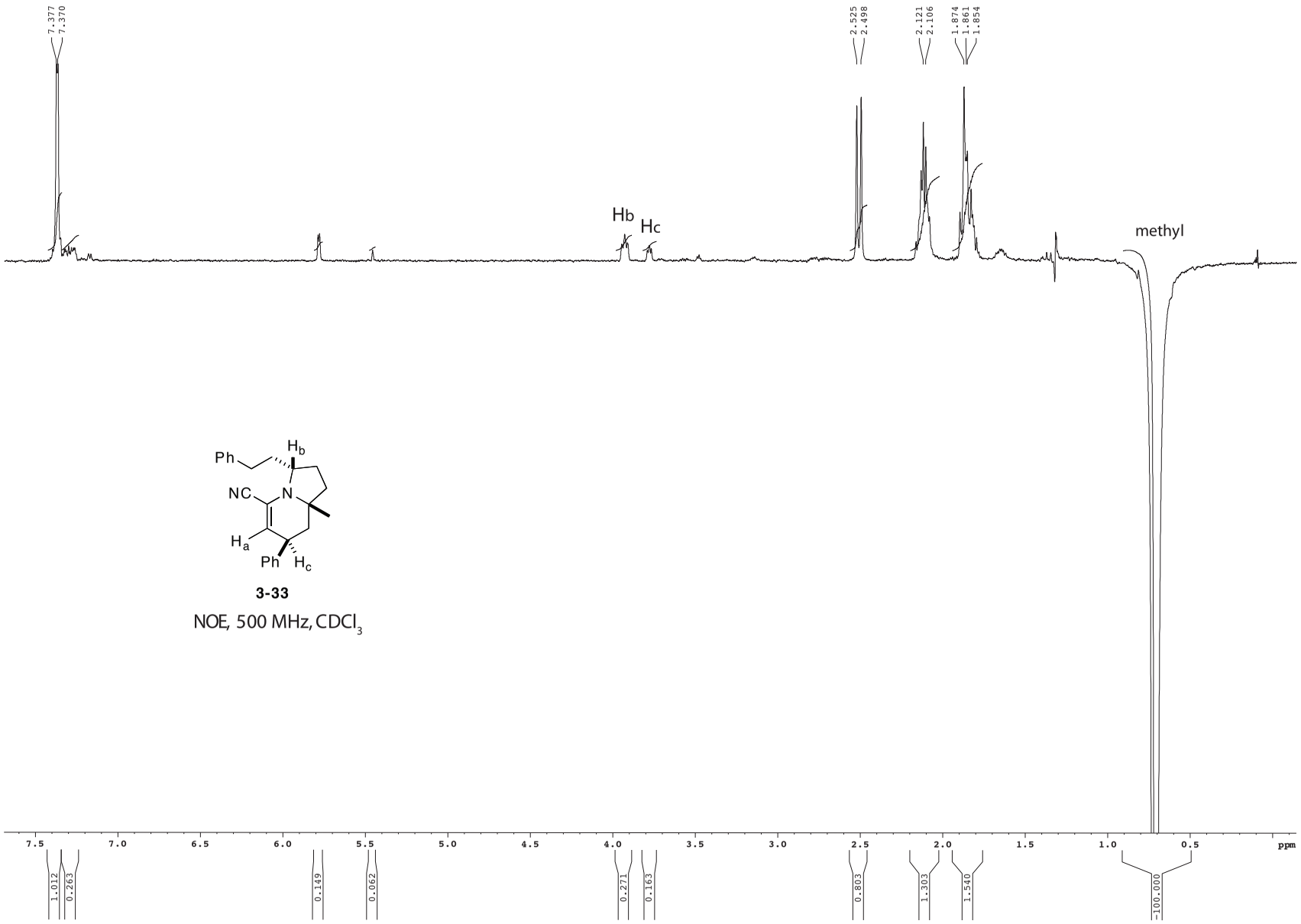


3-32

NOE, 500 MHz, $CDCl_3$

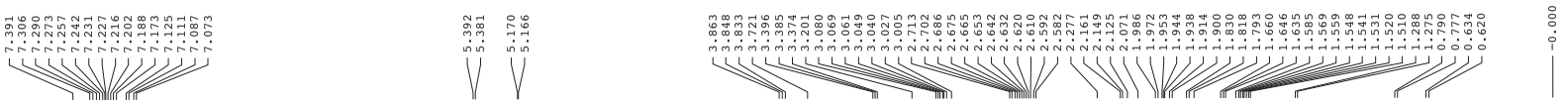

methyl
benzylic protons
Hb
Ph
NC
N
Ha
Hb
Ph
Hc
3-33
NOE, 500 MHz, CDCl3
ppm

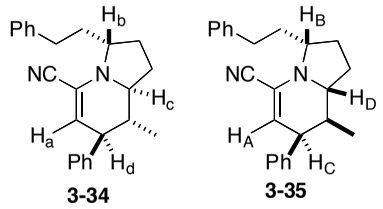

methyl
H_a
H_c
H_b
Ph
N
NC
H_a
Ph
H_c
3-33
NOE, 500 MHz, $CDCl_3$
ppm



3-33

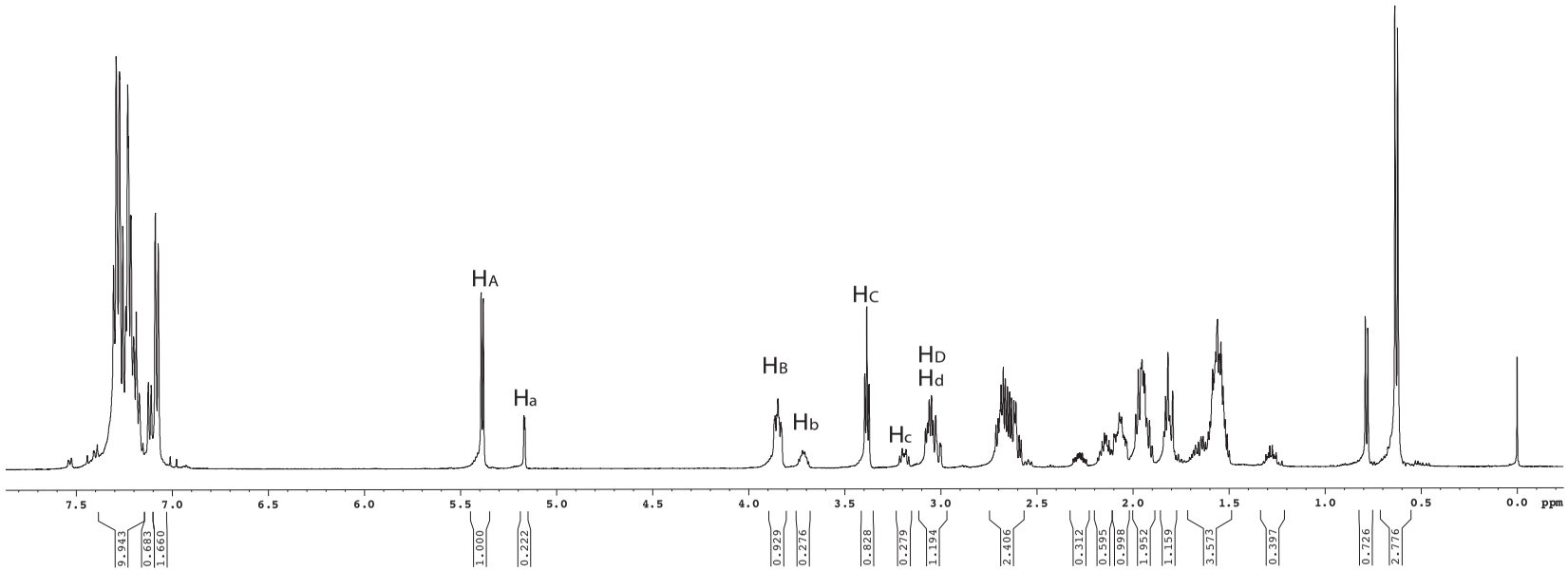
NOE, 500 MHz, $CDCl_3$

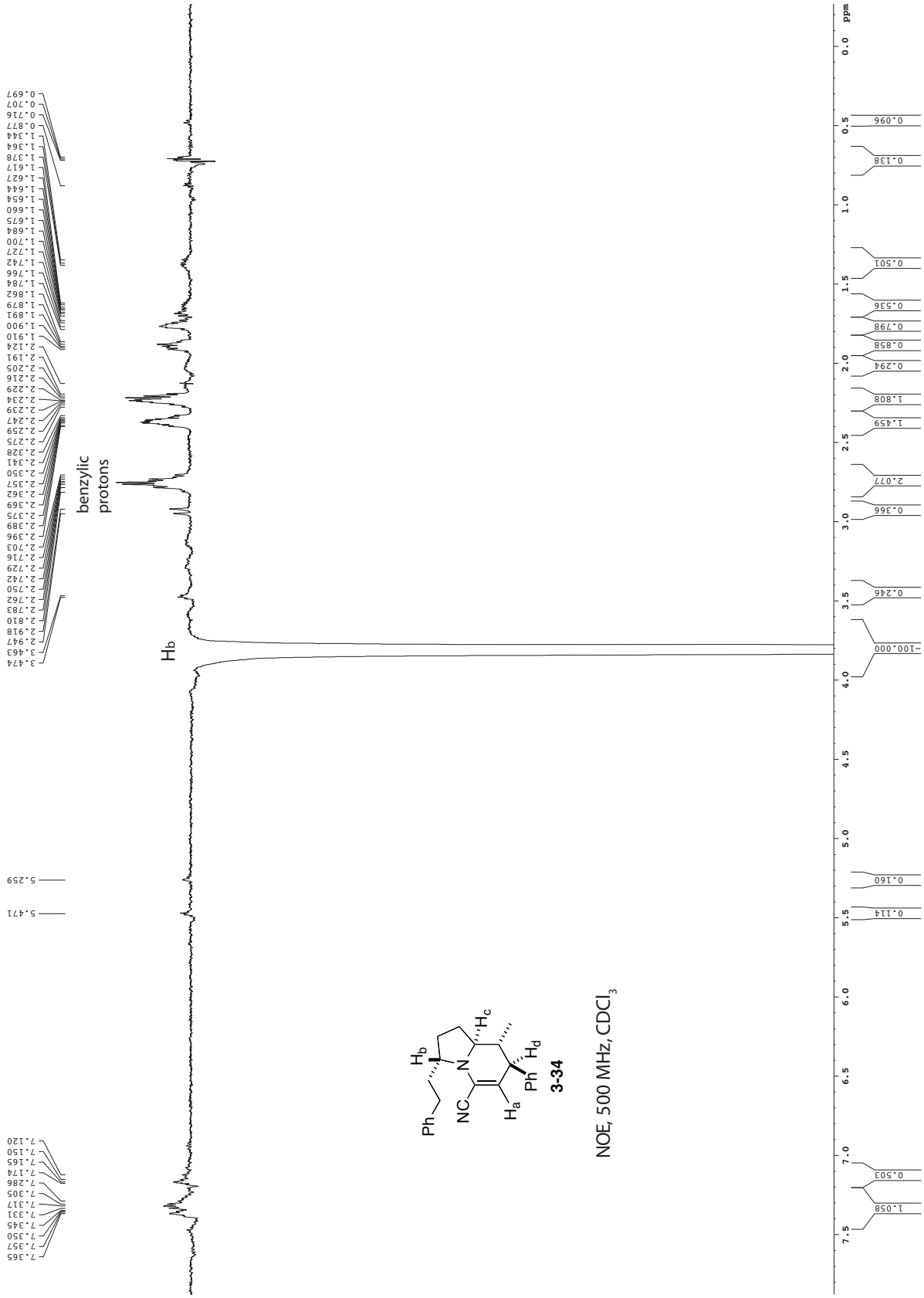


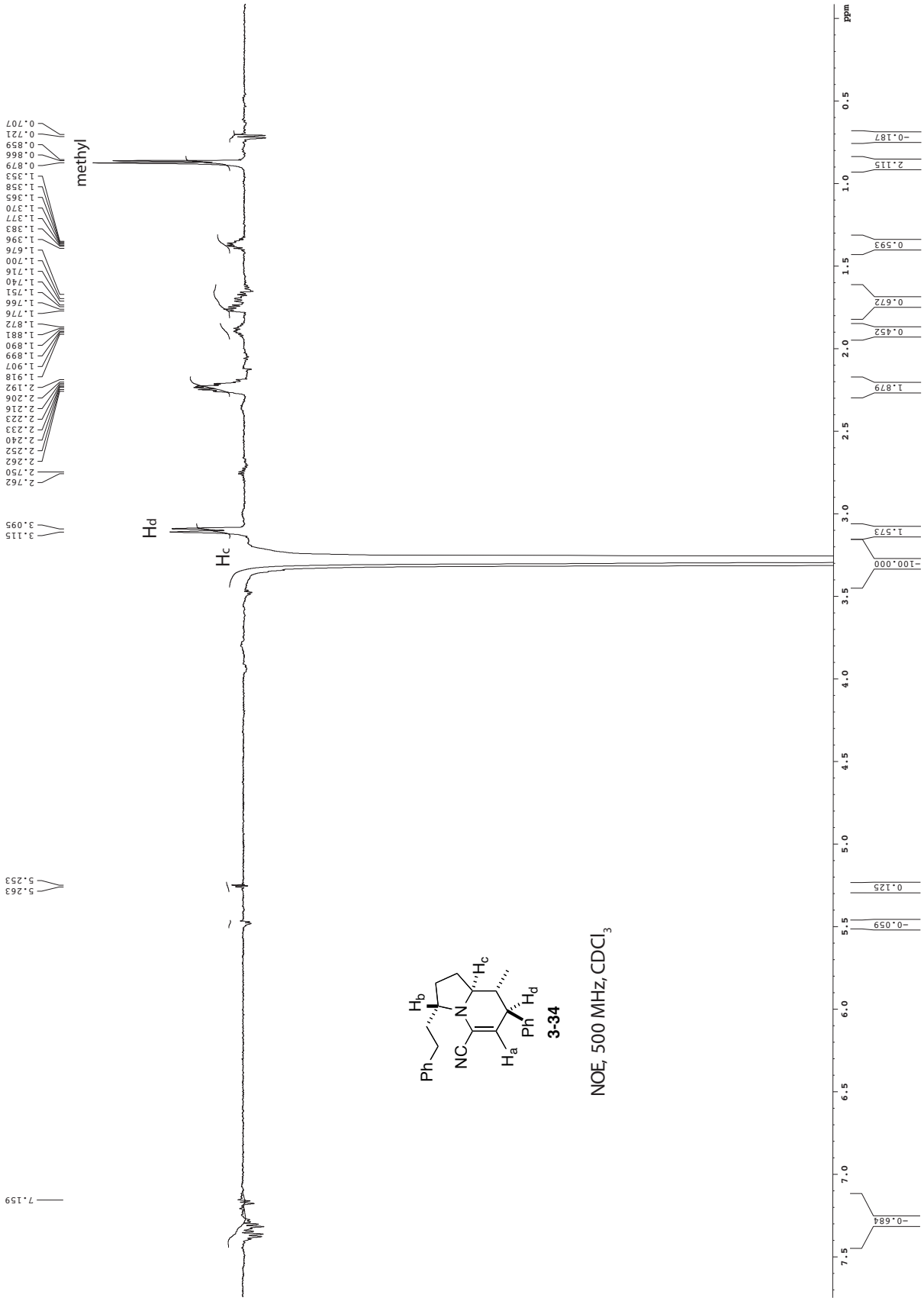


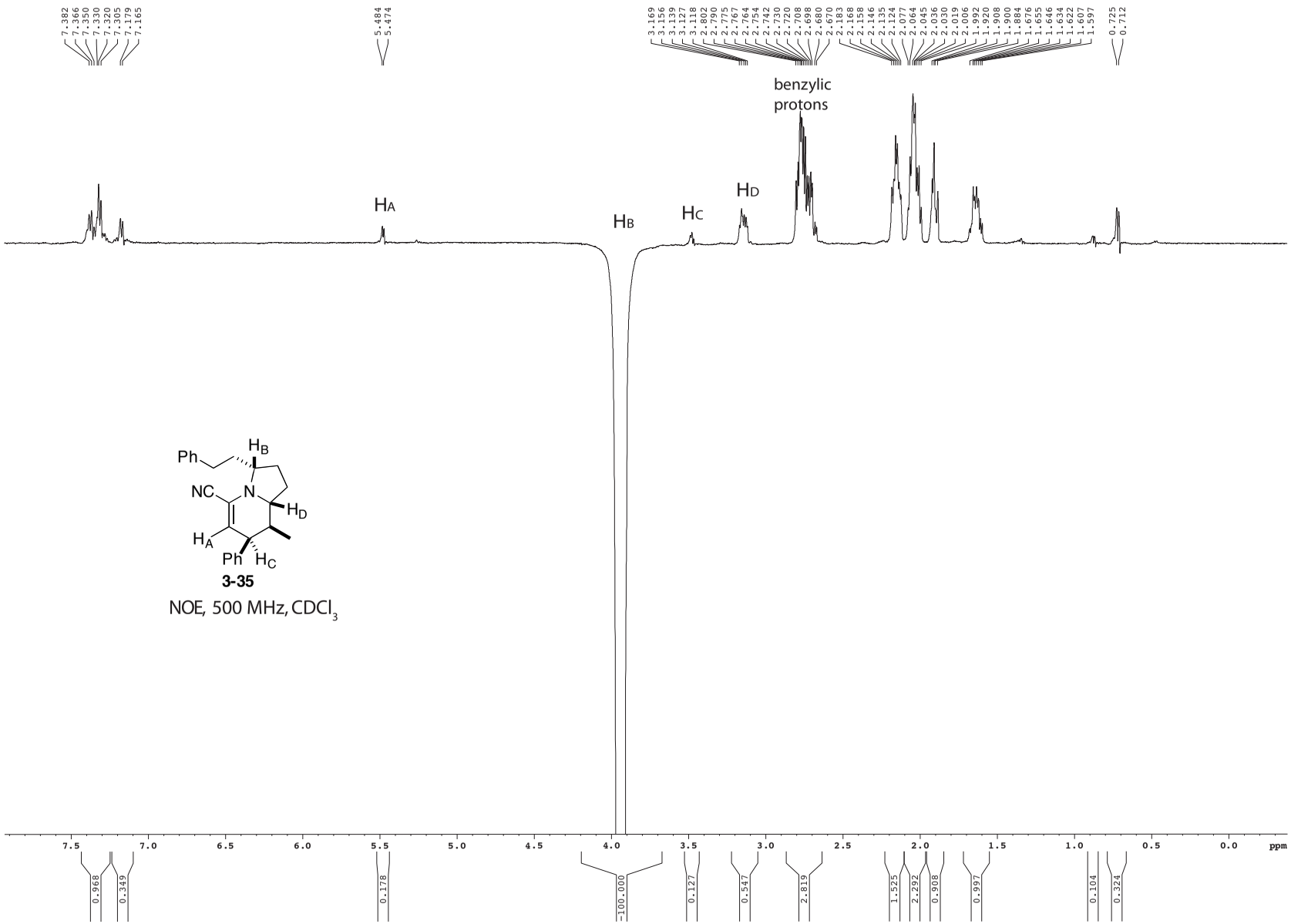
3-34 **3-35**

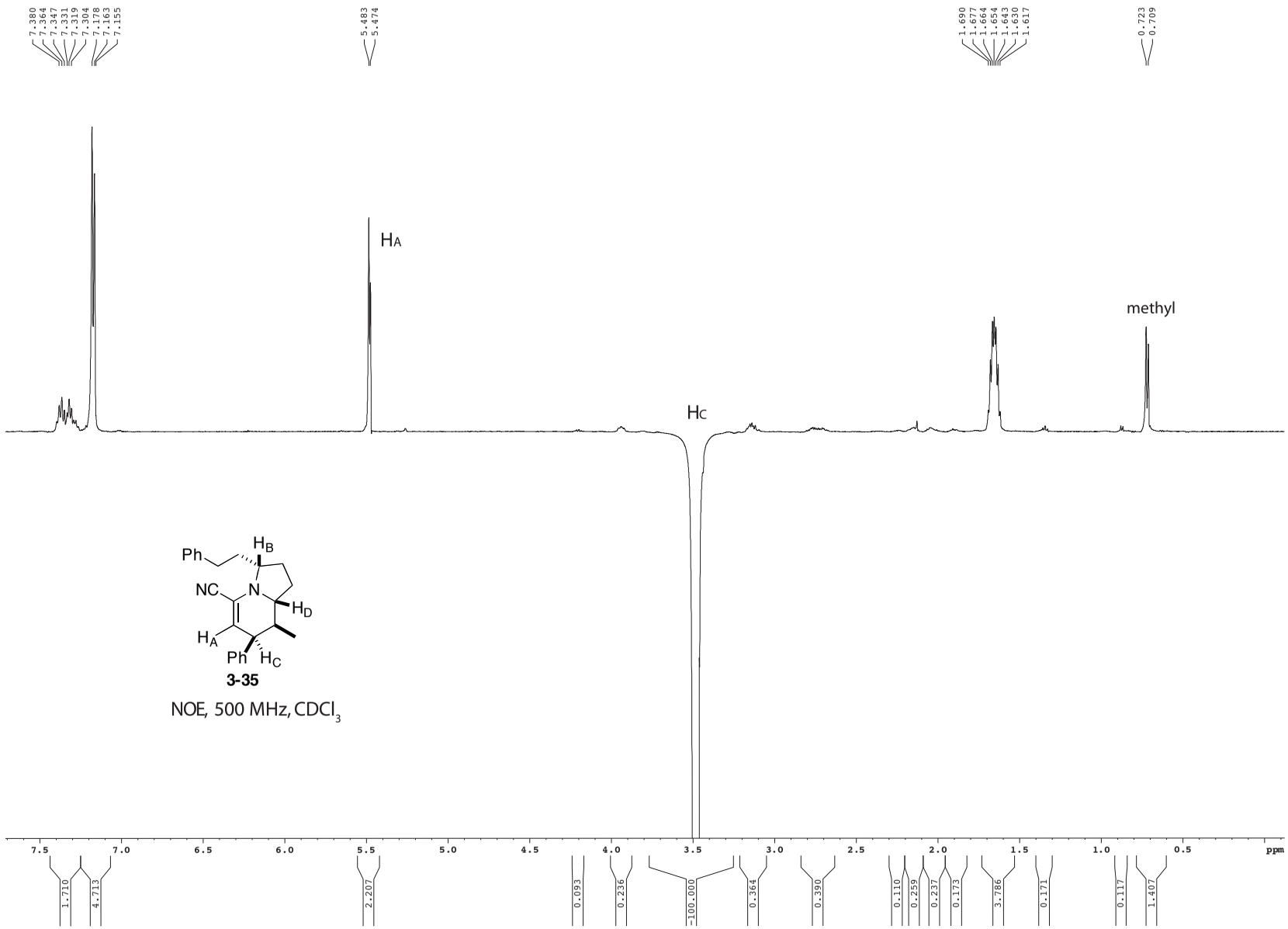
^{1}H NMR, 500 MHz, $CDCl_3$

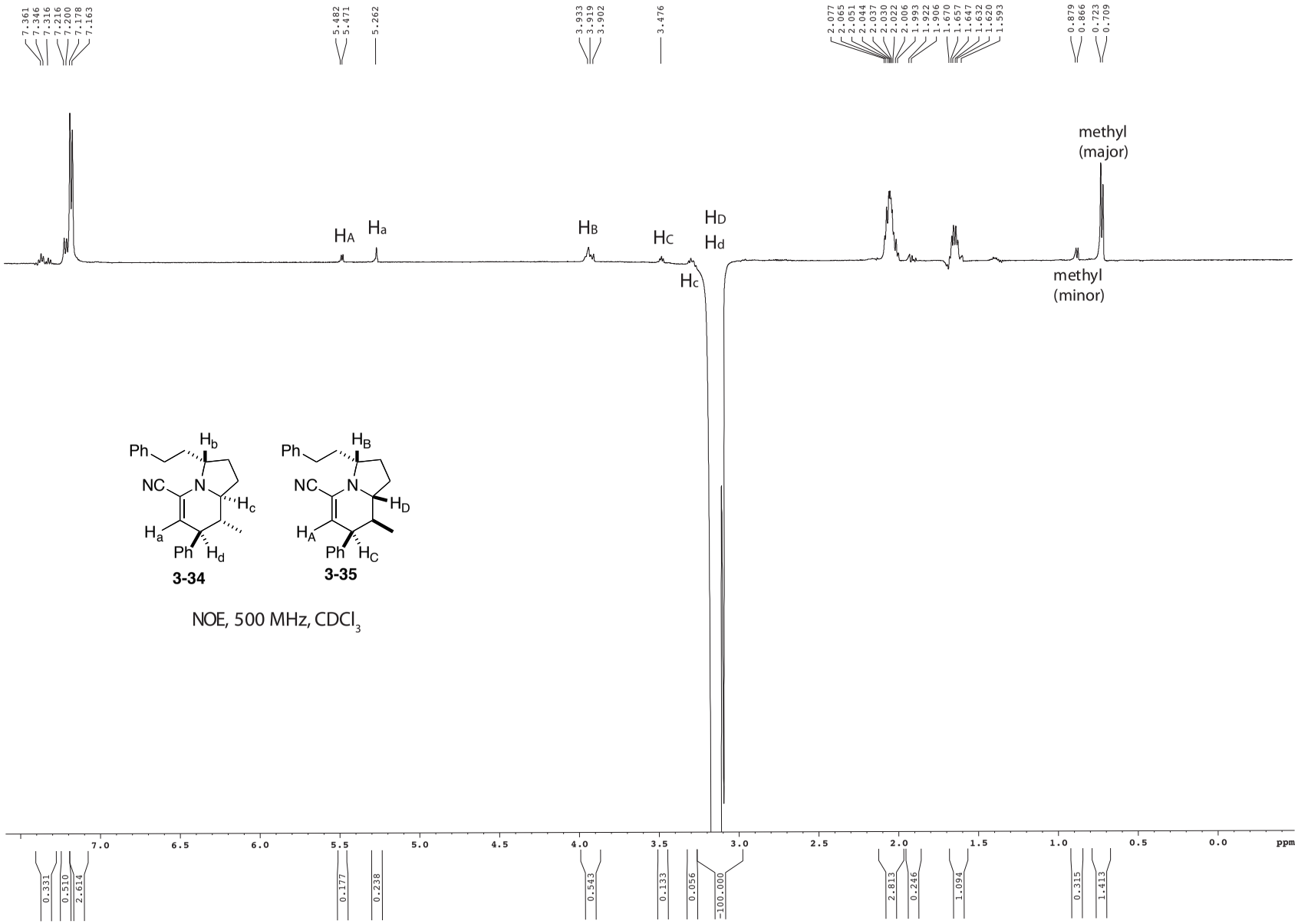


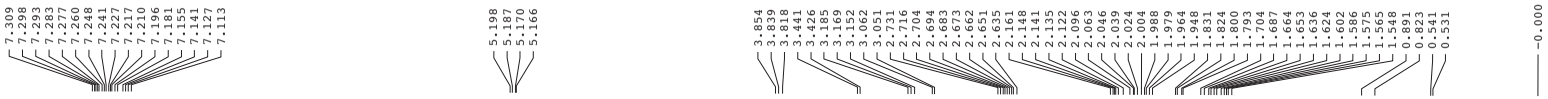

benzylic
protons
Hb
Ha
Hc
Hd
Ph
NC
N
3-34
NOE, 500 MHz, CDCl3
ppm

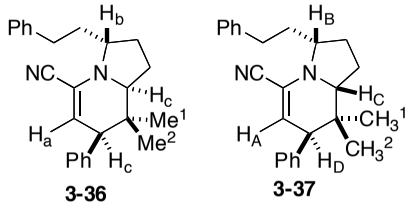

methyl
Hd
Hc
Hb
Ha
Ph
NC
N
Ph
Hd
Hc
3-34
NOE, 500 MHz, CDCl3
ppm


benzylic
protons
HA
HB
HC
HD
Ph
NC
N
HD
HA
Ph
HC
HB
3-35
NOE, 500 MHz, CDCl3
ppm

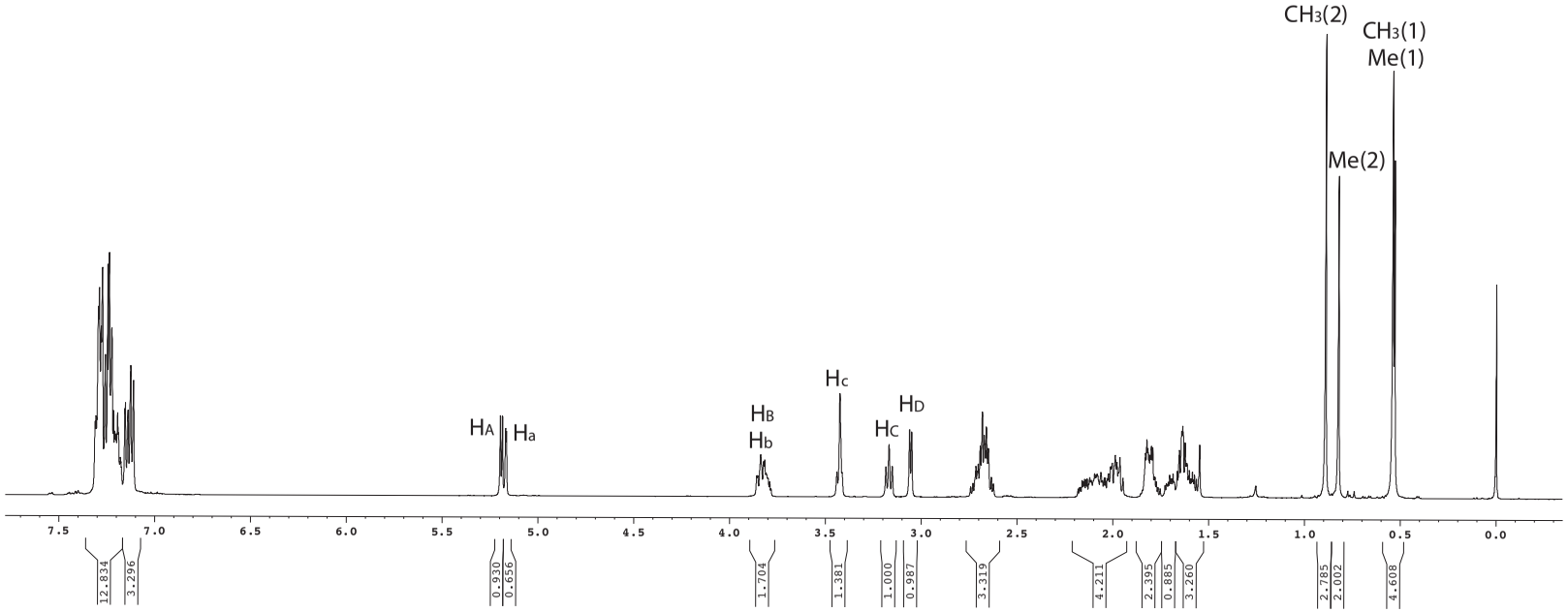

7.380
7.364
7.347
7.331
7.319
7.304
7.178
7.163
7.155
5.483
5.474
1.690
1.677
1.664
1.654
1.643
1.630
1.617
0.723
0.709
HA
HC
methyl
HB
Ph
NC
N
HD
HA
Ph
HC
3-35
NOE, 500 MHz, CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.710
4.713
2.207
0.093
0.236
-100.000
0.364
0.390
0.110
0.259
0.237
0.173
3.786
0.171
0.117
1.407

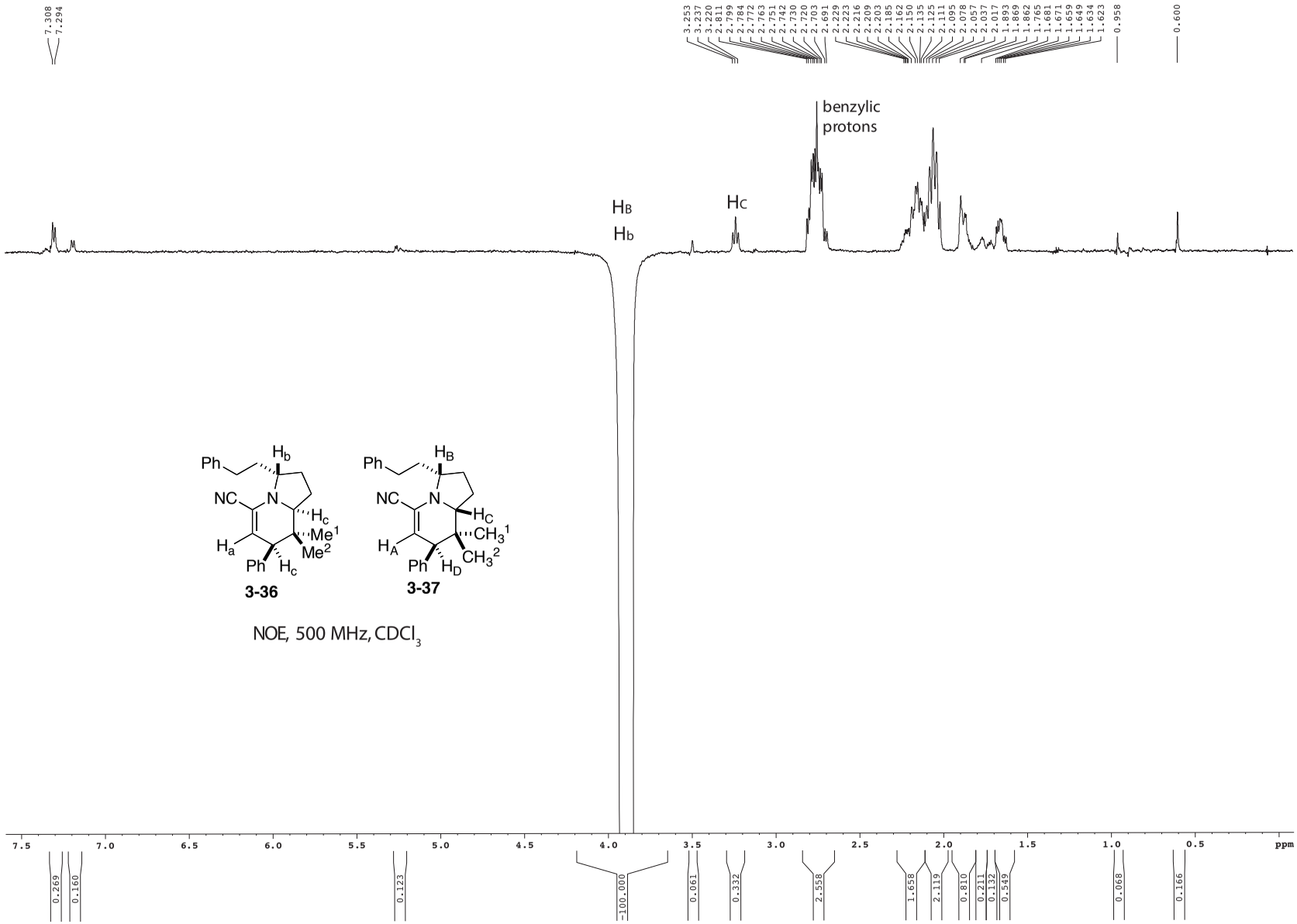

7.361
7.346
7.316
7.216
7.200
7.178
7.163
5.482
5.471
5.262
3.933
3.919
3.902
3.476
2.077
2.065
2.051
2.044
2.037
2.030
2.022
2.006
1.993
1.922
1.906
1.670
1.657
1.647
1.632
1.620
1.593
0.879
0.866
0.723
0.709
HA
Ha
HB
HC
HD
Hd
Hc
methyl
(major)
methyl
(minor)
Ph
Hb
NC
N
Hc
Ha
Ph
Hd
3-34
Ph
HB
NC
N
HD
HA
Ph
HC
3-35
NOE, 500 MHz, CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.331
0.510
2.614
0.177
0.238
0.543
0.133
0.056
100.000
2.813
0.246
1.094
0.315
1.413

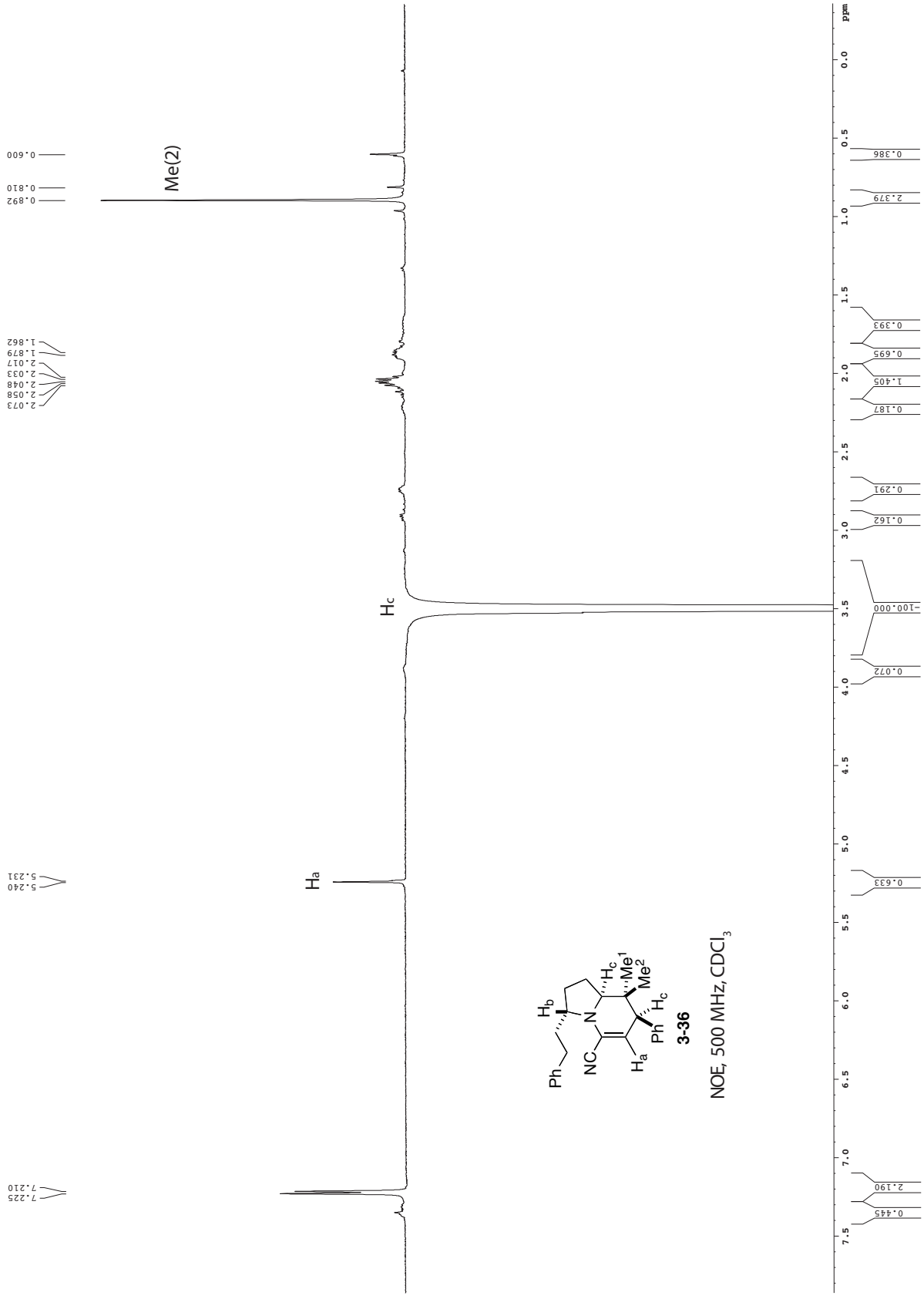


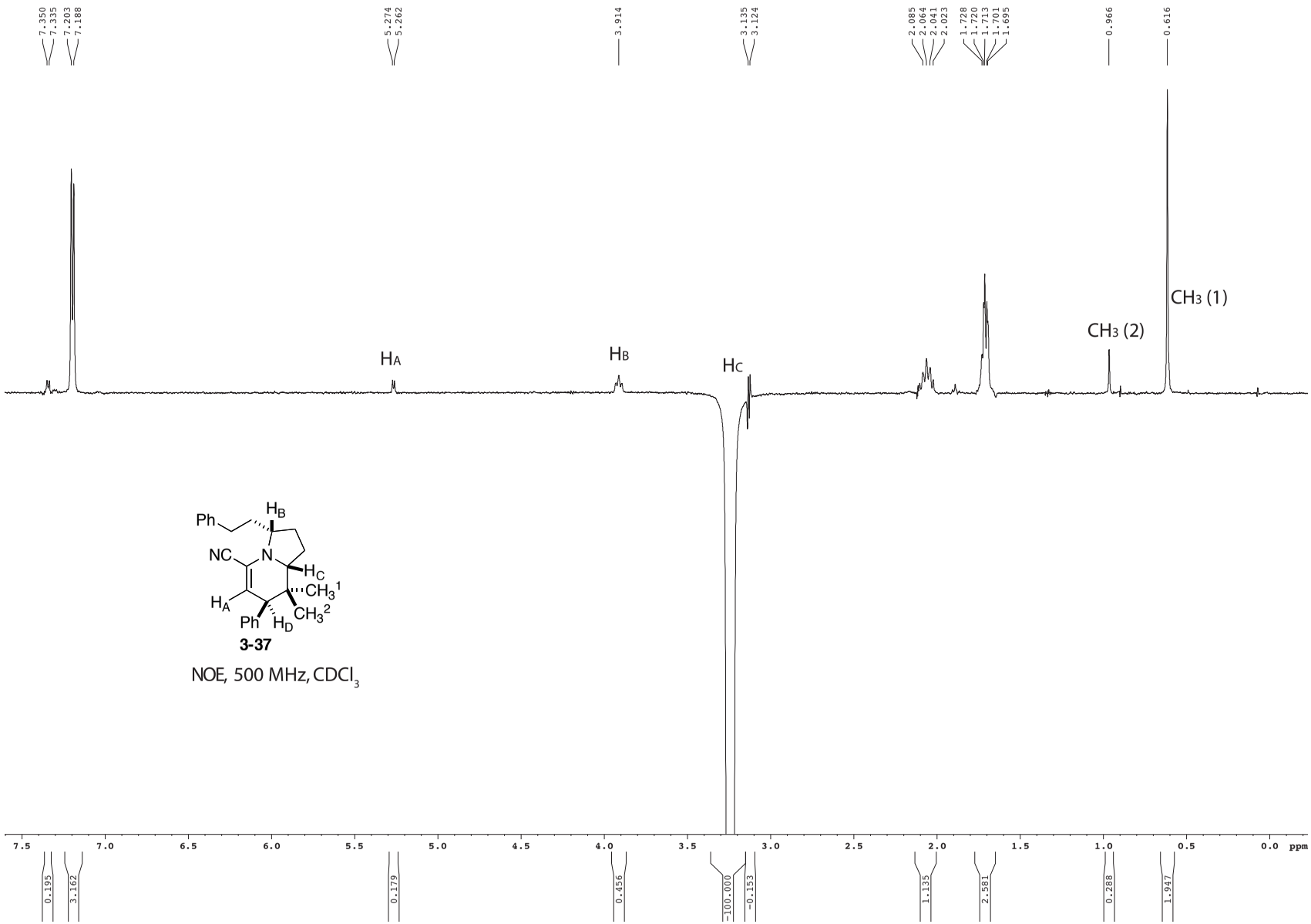


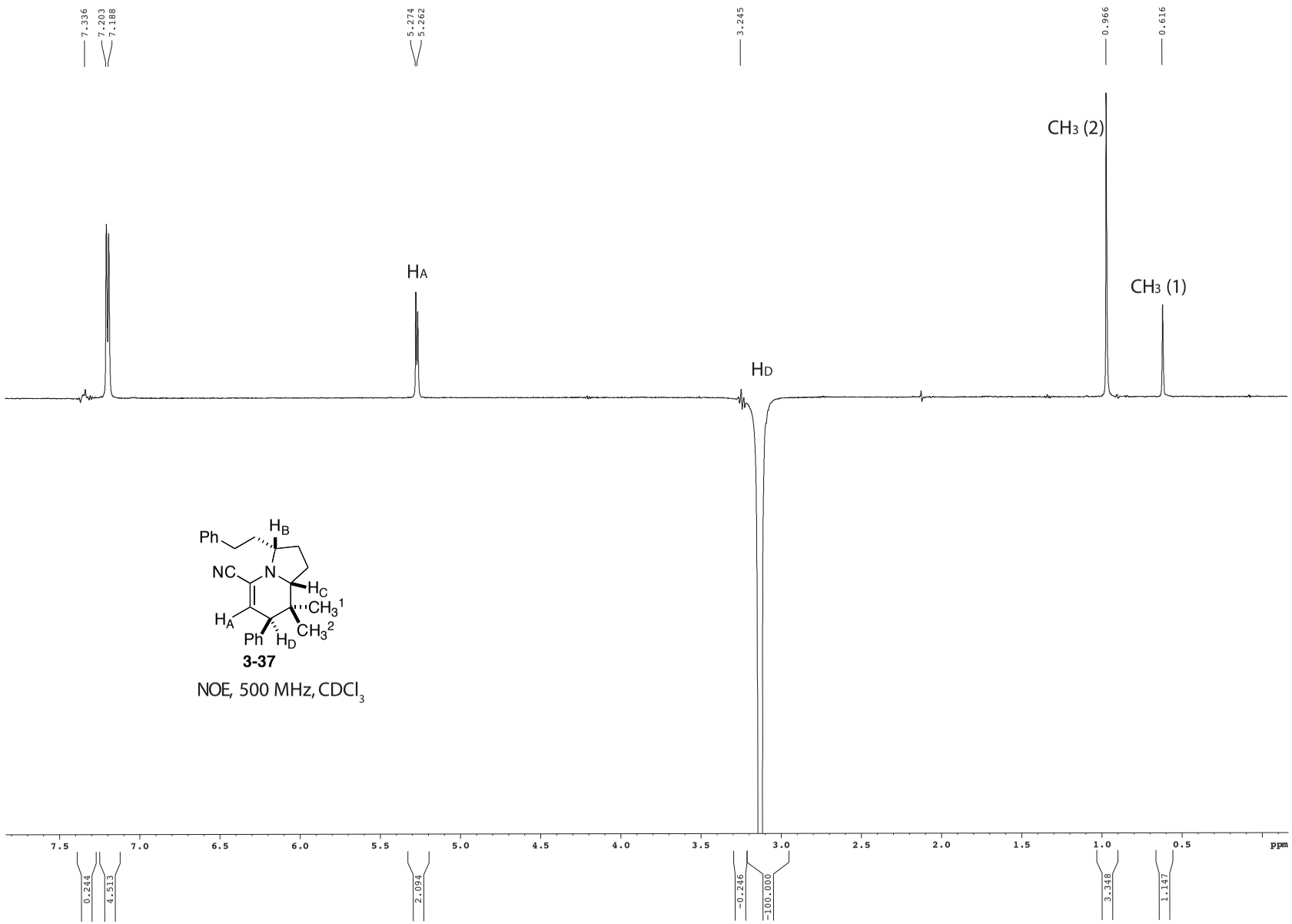
^{1}H NMR, 500 MHz, $CDCl_3$




benzylic
protons
HB
Hb
Hc
3-36
3-37
NOE, 500 MHz, CDCl3


Me(2)
Hc
Ha
Hb
Ph
NC
N
Ha
Ph
Hc
Me2
Me1
Hc
3-36
NOE, 500 MHz, CDCl3
ppm


7.350
7.335
7.203
7.188
5.274
5.262
3.914
3.135
3.124
2.085
2.064
2.041
2.023
1.728
1.720
1.713
1.701
1.695
0.966
0.616
HA
HB
HC
CH3 (2)
CH3 (1)
Ph
HB
NC
N
HC
CH3 1
HA
CH3 2
Ph
HD
3-37
NOE, 500 MHz, CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.195
3.162
0.179
0.456
-100.000
-0.153
1.135
2.581
0.288
1.947

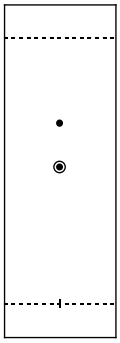


3-37

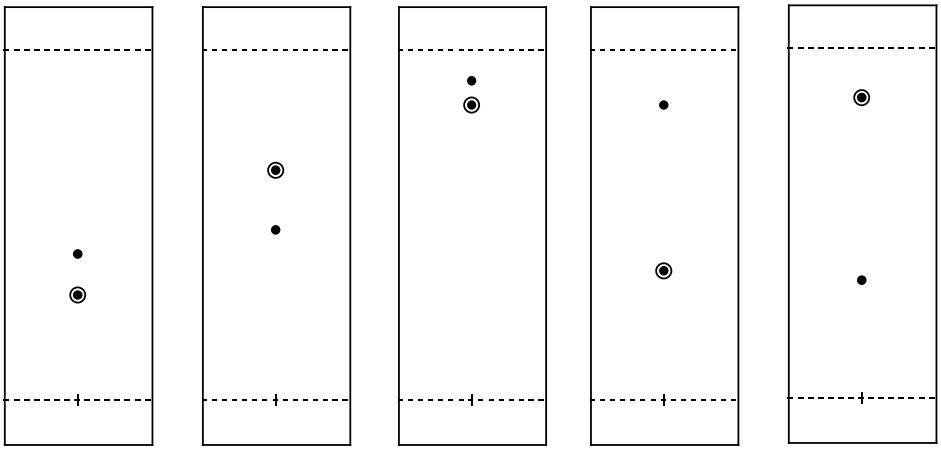
NOE, 500 MHz, $CDCl_3$

Thin Layer Chromatography

1) A student developed a TLC plate that was spotted with a mixture of a polar and nonpolar compound. The plate shown on the right was developed using 20% ethyl acetate:hexanes as the eluent. (Ethyl acetate is more polar than hexanes)

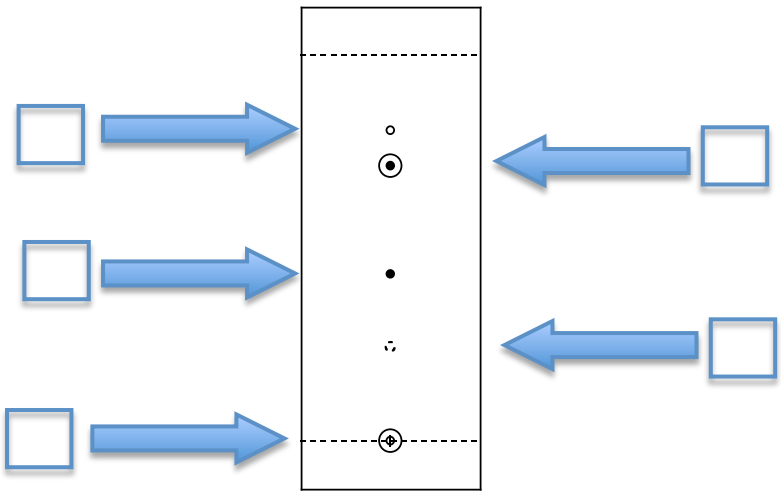


Instead of using 20% ethyl acetate:hexanes, 5% ethyl acetate:hexanes was used as the eluent. Circle the plate(s) that could be possible:



Check this box if you have no idea and just guessed

2) Rank the following spots/compounds in order of polarity. (1 = most nonpolar, 5 = most polar)



3) What did the dancers in white represent in the video?

a) the TLC plate
b) compounds
c) solvent
d) hydrogen bonding

4) Do you feel like you have a better understanding of TLC now that you have watched the video?

a) yes
b) no

5) Rate the helpfulness of the video in learning about TLC (10=very helpful, 1=not helpful at all):

1 2 3 4 5 6 7 8 9 10

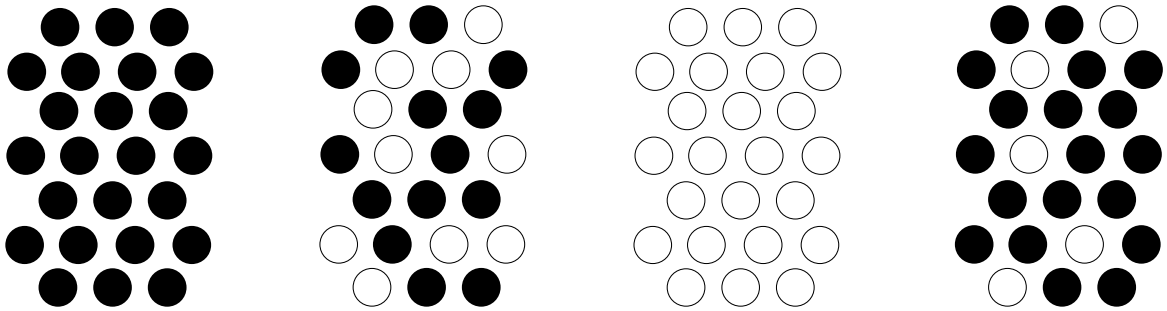
6) You would rather have learned about TLC through:

a) Traditional classroom lecture
b) This video
c) A traditional classroom lecture followed by this video
d) Other (Please Explain):

Please provide any comments about the video (you enjoyed it, ways to improve it, you hated it, if you thought the video was silly by useful, the dancers looked funny, anything!):

Melting Point

1) The black molecule melts at 110 ºC and the white molecule melts at 107 ºC. Rank the melting point of the crystal lattice shown below (1 = melts at the highest temperature)



☐ ☐ ☐ ☐

2) You have an unknown X that melts at 80-82 ºC. You perform a mixed melting to determine if unknown X is naphthalene (literature MP: 80 ºC) or vanillin (literature MP: 81 ºC). You figure out unknown X is vanillin. Circle the statement(s) that must be true:

(a) After mixing naphthalene with unknown X, the melting point decreases.

(b) After mixing naphthalene with unknown X, the melting point stays the same.

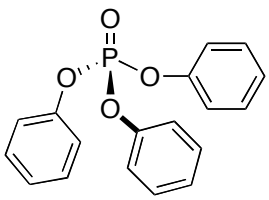
(c) After mixing naphthalene with unknown X, the melting point increases.

(d) After mixing vanillin with unknown X, the melting point decreases.

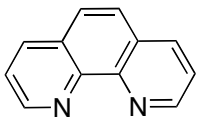
(e) After mixing vanillin with unknown X, the melting point stays the same.

(f) After mixing vanillin with unknown X, the melting point increases.

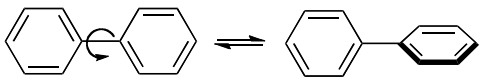
3) Rank the melting point of the following chemicals (1 = melts at the highest temperature)



triphenyl phosphate



phenanthroline



biphenyl

☐ ☐ ☐

4) What did the dancers in red represent in the video?

a) heat
b) compounds
c) impurities
d) the flask

5) Do you feel like you have a better understanding of melting point now that you have watched the video?

a) yes
b) no

6) Rate the helpfulness of the video in learning about melting point (10=very helpful, 1=not helpful):

1 2 3 4 5 6 7 8 9 10

7) You would rather have learned about melting point through:

a) Traditional classroom lecture
b) This video
c) A traditional classroom lecture followed by this video
d) Other (Please Explain):

Please provide any comments about the video (you enjoyed it, ways to improve it, you hated it, if you thought the video was silly by useful, the dancers looked funny, anything!):

Miscibility

$\Delta G_{soln} = \Delta H_{soln} - T\Delta S_{soln}$ (equation for free energy)
$\Delta H_{soln} = \Delta H_1 + \Delta H_2 + \Delta H_3$ (Hess's law)

1) Two liquids are miscible when ΔG_{soln} is

a) positive
b) negative

☐ Check this box if you have no idea and just guessed

2) Entropy always _____ when a solution is formed, therefore _____ is always _____.

a) increases/ΔG_{soln}/positive
b) increases/ΔG_{soln}/negative
c) increases/ΔH_{soln}/positive
d) increases/ΔH_{soln}/negative
e) increases/ΔS_{soln}/positive
f) increases/ΔS_{soln}/negative
g) decreases/ΔG_{soln}/positive
h) decreases/ΔG_{soln}/negative
i) decreases/ΔH_{soln}/positive
j) decreases/ΔH_{soln}/negative
k) decreases/ΔS_{soln}/positive
l) decreases/ΔS_{soln}/negative

3) When energy is added to a reaction, ΔH is _____. When energy is given off by a reaction, ΔH is _____.

a) positive/negative
b) negative/positive

☐ Check this box if you have no idea and just guessed

4) For the liquids to spontaneously mix at low temperatures the reaction must be _____; therefore ΔH_{soln} is _____.

a) endothermic, negative
b) exothermic, positive
c) exothermic, negative
d) endothermic, positive

☐ Check this box if you have no idea and just guessed

5) What did the dancers in yellow represent in the video?

a) energy
b) the compound
c) light
d) liquid

6) Do you feel like you have a better understanding of miscibility now that you have watched the video?

a) yes
b) no

7) Rate the helpfulness of the video in learning about miscibility (10=very helpful, 1=not helpful at all):

1 2 3 4 5 6 7 8 9 10

8) You would rather have learned about miscibility through:

a) Traditional classroom lecture
b) This video
c) A traditional classroom lecture followed by this video
d) Other (Please Explain):

Please provide any comments about the video (you enjoyed it, ways to improve it, you hated it, if you thought the video was silly by useful, the dancers looked funny, anything!):

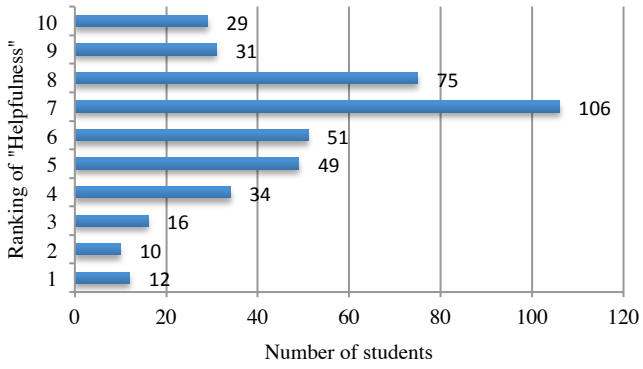
Results from the Surveys for Thin Layer Chromatography[1]

Question	# 1 (correct)	# 1 (incorrect)	# 2 (correct)	# 2 (incorrect)	# of students who admitted to guessed the correct answer for #1
Study Group (before video, pre-survey)	68	394	100	362	55
Study Group (after video, post-survey)	229	231	280	180	16
Control Group (pre-survey)	56	290	86	260	49
Control Group (post-survey)	44	301	94	251	32

Table A-2. Number of students that answered the question correct or incorrect.

- 403 out of 416 students (66%) gave the correct answer when asked what the dancer represented
- 353 out of 417 students (79%) said they felt they had a better understanding of the concept after watching the video.
- When asked how 416 students wanted to learn the concept:
  - 63 (15%) said traditional classroom lecture
  - 65 (16%) said the video
  - 268 (64%) said a combination of a traditional classroom lecture and video
  - 20 (5%) said they'd rather learn another way (A hands on experiment, a different more traditional/realistic video, lecture followed by reading, lecture/video/experiment combo, reading the textbook, peer tutor, and/or flip class.)

Students determined how helpful the video was in learning about the concept (10 = very helpful, 1 = not helpful)



Quotes from students about the TLC video:

"I think using dance as a way to represent the metaphor makes it easier to image what happens during the chemical process"

"The video was pretty dorky yet practical. The method in teaching such a topic about the TLC plate was surprisingly efficient"

"I thought the dancers were a good analogy"

"I thought the video was helpful and the dancers made the video interesting"

"I thought it was useful because I learn visually. It was helpful to see exactly how different eluents influence the movement of polar and nonpolar compounds"

"It was creative and instructional. It was also easy to understand"

“I thought the video was silly, but overall it was helpful. It was nice to have some help visualizing what was going on”
“I think the video was very clear in explaining the concept because it was explained in simpler terms and the dancers they used for a visual example really helped too”
“I’m a visual learner, so the dancers in the video helped me better understand what was happening with two different solvents”
“I thought that the visual representations were actually a lot more helpful than regular lectures in a classroom”
“Interesting video that captured my attention and was very informative”
“Funny, loved the use of the dancers. It was easy to understand, was straight to the point”
“I enjoyed it! It made it easy to picture and remember, rather than by just reading about it”
“I think the video was very silly, but because of that silly factor, I enjoyed it much more than I would a lecture”
“I liked the creativity and visual aspect of the video. I also liked it because it was funny, and funny things stick into my head better”
“Having dancers and colors were visually entertaining and educational”
“The video is interesting. It makes chemistry easy”
“I really loved the video, it was pretty entertaining to watch, made me want to watch it again”
“I thought this video was very creative and engaging because although it is 8am in lab, I still enjoyed watching“

Results from the Surveys for Melting Point[1]

Question	# 1 (correct)	# 1 (incorrect)	# 2 (correct)	# 2 (incorrect)	# 3 (correct)	# 3 (incorrect)
Study Group (before video, pre-survey)	1	414	72	343	38	377
Study Group (after video, post-survey)	114	304	221	197	140	218
Control Group (pre-survey)	3	412	100	315	33	382
Control Group (post-survey)	1	416	105	312	48	369

Table A-3. Number of students that answered the questions correct or incorrect

- 403 out of 418 students (96%) gave the correct answer when asked what the dancer represented
- 353 out of 416 students (85%) said they felt they had a better understanding of the concept after watching the video.
- When asked how 415 students wanted to learn the concept:

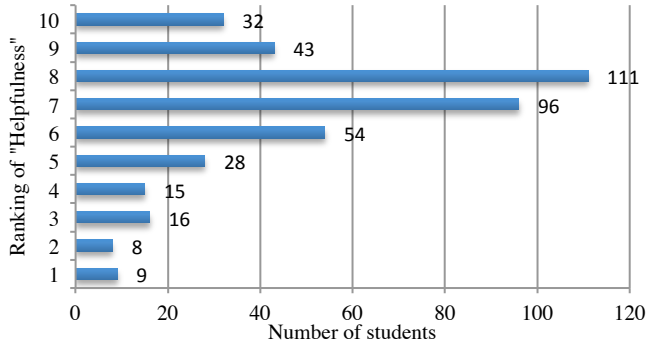
  63 (15%) said traditional classroom lecture

  107 (26%) said the video

  235 (57%) said a combination of a traditional classroom lecture and video

  10 (2%) said they'd rather learn another way (A powerpoint presentation, a different more traditional/realistic video, a live dance performance, textbook, note card of generalized things to remember, classroom discussion and the video, have the students dance)

Students determined how helpful the video was in learning about the concept (10 = very helpful, 1 = not helpful)



<u>Quotes from students about the melting point video</u>:

"I think it's a creative way to teach about melting point"

"I enjoyed the video, it was pretty funny, but it was informative too"

"The dancers provided me a great visual of melting point and made it easier for me to understand"

"The video was silly but that is why I'll remember the information. It was helpful"

"I thought the video was very creative and it really gave good visual examples as to how melting point works"

"I enjoyed the video because the dancing was a nice way to demonstrate melting point. They did look funny but it made it more enjoyable"

“It was an excellent way to visualize the process. Every note was thoroughly addressed and understood”
“Yes, the video was silly but engaging to help us. Sometimes, entertainment is the best learning”
“It was pretty memorable and very effective”
“Video was quite entertaining and helped give me a visual way of understanding in a creative way”
“It was a weird video which makes you remember the facts easier”
“The video was both educational and entertaining”
“The video grabbed my attention better than traditional classroom setting would have”
“It was entertaining and got me more excited for the topic”
“The video was very informative”
“The dancers provided me a great visual of melting point and made it easier for me to understand”
“It was a silly video but the message and purpose of this video was understood and apparent”
“It was actually really funny, but it helped me understand melting point”
“It’s different from a regular lecture, so it’s something I would remember better”
“I enjoyed the visual representation of the dancers posed in the video. It made it easier to understand the concept of melting point”
“Helpful learning tool”

Results from the Surveys for Miscibility[1]

Question	# 1 (correct)	# 1 (incorrect)	# 2 (correct)	# 2 (incorrect)	# 3 (correct)	#3 (incorrect)	#4 (correct)	# 4 (incorrect)
Study Group (before video, pre-survey)	256	146	153	249	376	26	243	159
Study Group (after video, post-survey)	376	15	286	105	376	15	291	100
Control Group (pre-survey)	241	179	150	270	394	26	280	140
Control Group (post-survey)	278	141	189	399	399	20	270	149

Table A-4. Number of students that answered the question correct or incorrect

Question	# 1	#2	# 3	# 4
Study Group (before video, pre-survey)	157	n/a	35	39
Study Group (after video, post-survey)	0	n/a	1	3
Control Group (pre-survey)	144	n/a	26	38
Control Group (post-survey)	86	n/a	18	22

Table A-5. Number of students that admitted to get the question correct by guessing. After watching the video, less students were getting the correct answer simply by guessing.

- 359 out of 391 students (92%) gave the correct answer when asked what the dancers represented
- 302 out of 388 students (78%) said they felt they had a better understanding of the concept after watching the video.
- When asked how 391 students wanted to learn the concept:

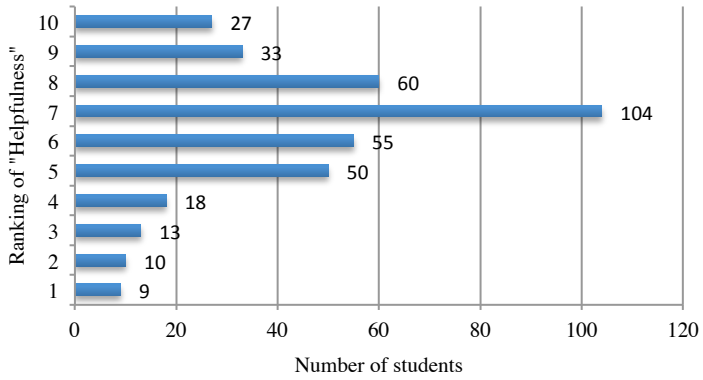
  90 (23%) said traditional classroom lecture

  70 (18%) said the video

  217 (55%) said a combination of a traditional classroom lecture and video

  14 (4%) said they'd rather learn another way (Reading a textbook, a more straight forward video, demonstrations, interactive simulation, simple handout, powerpoint with lecture, combination of lab and lecture, podcast on course website,)

Students determined how helpful the video was in learning about the concept (10 = very helpful, 1 = not helpful)



Quotes from students about the miscibility video:
"It was entertaining and a fun way to look at miscibility"
"Funny visuals and it did explain the concepts pretty well"
"It was a very unique way to learn about miscibility"
"It was a visual representation of how it works. Students whom are visual learners will appreciate this style of teaching"
"It was hilarious. A good way to learn material in a different way"
"Video seemed silly, but that is what makes everything in it stick, so overall it is a helpful video"
"I enjoyed it because it was able to break down a concept very well and easy to understand"
"This is really great! Wish I had this resource for Chem 1B. Would've done much better than I did and would've actually understood it."
"I thought the video was interesting and helped me remember because it gave a visual that I will always see when miscibility is brought up."
"I thought the video was a little silly, but it helps a lot! Videos and podcasts that provide extra help after lecture are really useful and this particular video was more interesting than most things."
"I liked it very much, as concepts were simplified and made it easier to understand"
"I enjoyed watching the video, it helped me understand/visualize. Definitely silly but very useful"
"It was a lot better than lecture…"
"I thought of using dancers to help convey the idea was a clever technique. It made learning enjoyable to watch."
"It was really cheesy, but I actually retained the information"
"The video was helpful, even though it was silly. It made learning enjoyable"
"Very creative and interesting way to learn about miscibility. I definitely engaged in the video"
"It was a very random way to teach a lesson but because it is so absurd and unusual, I won't forget it. More DanceChemistry!"

[1] The number of students from the pre- and post-survey varied slightly because students were absent one of the days that the survey was administrated. Some students also chose not to respond to the more qualitative questions about how they felt about the DanceChemistry video.