FORAYS INTO THE SYNTHESIS OF ZOANTHENOL: INTRIGUING PATTERNS IN REACTIVITY AND SELECTIVITY

Thesis by

Jennifer L. Stockdill

In Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

California Institute of Technology
Pasadena, CA
2009
(Defended 5 December 2008)
DEDICATION

To my parents, Dave and Lucy Stockdill, who have sacrificed so much for me.

To my sister and brother, Teresa Barth and Jon Stockdill, who have been role models to me all of my life.

To my eighth grade science teacher, Mary Alice Robinson, who sparked a passion that has not died.

Finally, to my nieces and nephews, Hudson Barth, Deirdre Stockdill, Landen Barth, Jonah Stockdill, and Zoe Barth, who have provided the extra motivation to finish my Ph.D.
ACKNOWLEDGEMENTS

...It is impossible to start....

It cannot be argued with that the most influential person in my graduate career has been my advisor, Brian M. Stoltz. Brian’s passion, guidance, and discipline have been indispensable to my growth as a scientist and as a person over these past five and a half years. I am especially grateful to Brian for his devotion to his students’ education and success. I have not heard of another professor who goes so far out of his/her way to make sure students are prepared for whatever the next step in their journeys may be. Also, Brian introduced me to my best friend EVER, TLC. After all, it is the fastest, cheapest, easiest way to obtain meaningful information about what’s going on in your reaction flask!

I am especially indebted to my thesis committee members, who have been simply unreal. Dennis Dougherty, my committee chair, has done a surprising job of keeping Harry in line, not to mention the insights he has provided in discussing my ideas and the depth to which he forces me to think. Harry Gray has been a constant source of support that has proven to be truly invaluable over the past two years when life has seemed so overwhelming. Bob Grubbs, the most recent addition to my committee has been asking me regularly how my research is going for years (I always regret not having a more cheerful reply, but the inquiries have meant a lot to me), and he always remembers to tell me when he’s going climbing and I have to stay in lab! In all seriousness, all of my committee members have been very gracious and generous with their time, ideas, and recommendation letters. Thank you so much to all of them.

I have had the great pleasure of working on my project with Dr. Doug Behenna and Dr. Andy McClory. Doug was the single most influential person on my development as a
bench chemist. He taught me everything from what a TBS group is, to how to run a column, to the true meaning of scale-up. His hard work and friendship over the past years have been critical. I am grateful to Andy for helping me to learn that there is more than one way to approach a problem. He is a brilliant scientist, and I am sure he will be an amazing professor.

The various members of the Stoltz group have provided a diverse, if occasionally tumultuous, environment that has not only shaped me as a chemist, but also as a person. Through all of the ups and downs of the 72+ hours/week that we spend together, I wouldn’t replace any of the people I have had the opportunity to work with in the lab. The early lab members were instrumental to me in learning techniques and in how to think about chemistry. I am especially grateful to Eric Ashley, Eric Ferreira, Doug Behenna, and Raissa Trend for their advice in my early years. Toward the middle and through the end of my graduate career, I had the great fortune of becoming close friends with Dave Ebner and Ryan McFadden, who were both willing to talk endlessly with me about my chemistry and who always tried the ideas that I suggested for their work. They, of course, have both ditched me, and I miss them dearly. (Congratulations to RMAC on the birth of his son, Nathan!! And Dave...you can’t escape! I’ll be in NYC soon.) I am more and more grateful to Dan Daspi every day as I write my thesis. Dan is so thoughtful in always trying to make the annoying parts of lab life run more smoothly. He has created a macro for everything you might need to do with a spectrum, and I think I’d still be trying to figure out how to get the things into my thesis right now if it weren’t for him. My classmates are an awesome crew. I’m grateful to JT, who is a fountain of info from what’s the deal with my NMR or the pKa of chemical X to what’s the last step of the Rubik’s cube algorithm. (Congratulations to JT on the birth of his daughter, Marie!!) Mike Krout always has what I’m looking for, whether it be a reagent or a procedure, and his generosity with both is appreciated. Also, I’ve always been grateful to
him for being so nice during group sports...I suck at most of them, and he is always patient. Mike Meyer has been a great friend over the years, and he will always hold a special place in my heart. Which brings me to Jenny Roizen...Jenny, I'll put your part at the end. The fou...fifth years are an eclectic bunch, that I have loved having around for the past four years. Nat Sherden has always been good to me, from bringing my mail in that ended up at his house to walking out of his way to walk me home when it’s late at night, to apologizing when I have done something wrong, his kindness is overwhelming. Also, the emails...I love the emails. I hope I don’t get taken off the group list right away because I will miss the misspelled sarcasm-rich frustrations. John Enquist is one of the most dedicated people I’ve known. It has been fun trying to break through his wall of seriousness (the trick is mint-chip ice cream!), and his dry sense of humor really gets me laughing sometimes. I have really enjoyed Kevin Allan’s company as a baymate (briefly) and on years of coffee runs. I will always cherish the memory of late night flash columns listening to Ok Go, and I really admire his enthusiasm in the lab. Also, thanks for the cookie. Sandy Ma is one of the more unusual (in a good way) characters I’ve met. (DOGGIE!) She always makes me laugh and has the most quotable quotes. Brinton Anna Seashore-Ludlow was a fun baymate and is a great friend. I have missed her often since she moved to Sweeden. I’ve enjoyed getting to know Pam Tadross better over the past 9 months or so, and I’m sad that it took so long. She is a really thoughtful person and devoted friend. Chris Gilmore has always cracked me up. He’s a great person to talk about life with, and lately I’ve enjoyed talking Obama with him as well. It’s been awesome to have Hosea in the lab. He has such a different perspective from the status-quo, it’s always fun to see what he thinks. I’ve really enjoyed Narae’s company over the past few years. She is a genuine and sweet person, and I’ve grown to expect her in lab on Saturday over the past 6 months. I always thought she was joking when she said he hobby was sleeping, but she seems to be in lab the rest of the time! :P I’ve grown to
really enjoy having Allen Hong in 264, and it will be really sad to say goodbye. I’m thankful for all the candy and especially for his concern...he always wants to know how you’re doing when he asks. Of course, I’ll miss my secret admirer, aka Hahvard, aka Matt Winston. Matt has been a great cheerleader in my thesis effort and his support is really appreciated. Also, he cheers Jenny up, which cheers me up! The first years in the group are a hilarious bunch, and I regret that I won’t have the opportunity to get to know them better. Nathan Bennett, my newest baymate, always has something nice to say, and he is very encouraging, even to himself... “Alright, self...” Jonny Gordon is just too cool for school (but he comes anyway). I dig the purple sweatband and the blue glasses. Alex Goldberg is our newest member, and he seems to share my sarcastic sense of humor. Finally, there are the postdocs. There have been many...I’m especially grateful to Amanda Jones, who has been a really good friend, and is always a pleasure to have in lab, but most importantly, hosts the poker night (no boss allowed!). Jan Streuff has been a fun companion over the past year, and I will miss him when he goes back to Deutschland. Also, Corinne Baumgartner has been a fun exercise buddy, and Christian Defieber always tried to speak German with me. If it weren’t for Nolan McDougal, I would not be able to say that I’ve walked from campus to Roscoe’s, or worse, I might not know how to properly eat bread at a nice dinner! I’m grateful to him for the fun memories and for introducing me to scallops. I mentioned Andy McClory briefly, but I need to mention here that he is one of the more loyal friends a person could ask for, and I really enjoyed his friendship. A recent addition to the lab, Chris Henry, has fast become one of my closest friends, and I am very thankful to have met him. Thanks also to Xiaoquing Han (X-Dog), Andy Harned, Haiming Zhang, and Kousuke Tani for their kindness and advice.

I need to make a separate paragraph here for my baymates. Eric Ashley was my first baymate, and I am ever grateful to him for all that he taught me those first few years.
Also, I wouldn’t know important things like “what ever happened to a good old fashioned passionate *%&-whuppin’, getting your shoes, coat and your hat tooken.” Brinton Seashore-Ludlow is one of those people that you just love right away. We had lots of fun hiking and going to yoga, and of course running collumm-collumnns!! Enough cannot be said about Thomas Jensen, who among other things was the first baymate I had who liked *all* the same music as me. We had a blast jammin’ in the lab and talking chemistry. Not to mention playing 10:1 with Dave!

I would like to thank Thomas Jensen, Dave Ebner, Chris Henry, and Brian Stoltz for proofreading *all* of my thesis. Amanda Jones, Doug Behenna, Kevin Allan, Jenny Roizen also edited chapters. Jenny, thanks for doing it at the last minute with no notice. I am especially grateful to Chris Henry for his help with numbering compounds and to Dave Ebner for making my table of contents and list of figures. Dave is also the only person who proofread my whole thesis twice (or was it three times?). He must be really bored over in New Jersey waiting to start his postdoc! ;) Thank you all so much. This document would be a mess without you.

In addition to the outstanding members of the Stoltz group, I have been warmly welcomed by the Grubbs, Bercaw, Gray, Dougherty, and Reisman labs. To thank each of the people in these groups would be overwhelming, but they are all truly appreciated, and I look forward to seeing them in the future.

Amazingly, I managed to meet some people outside of the department, and it turns out that many of them have been among my most critical and constant supporters. I would not be the same person without the friendships of Justin Bois, Raviv Perahia, Hernan Garcia, Tristan Smith, Anna Folinsky, Erin Koos, Nhat Vu, Nate Bode, Vikram Deshpande, Eric Peterson, Lucia Cordiero, Heidi Privett, Crystal Shih, Jeff Byers, Steve Baldwin, Dan Grin and Harmony Gates. You guys have all been truly amazing friends, and I am so thankful for all the times you’ve scraped me off the ground and reassembled
me into a human again. My move to the West Coast would not have been conceived of without Joe Polidan, and my last year of college would have definitely not been as fabulous without Sheila (a.k.a. Pony 2) Gradwell. Boo Shan Tseng and Hari Shroff were indispensable companions in Argentina/Chile. Likewise, Mike Olsen was a blast to have along in Costa Rica. It was a pleasure spending two weeks with each of them in paradise.

Those memories bring me to Tristan Ursell, who was my companion for three of the most challenging, yet adventure-packed years of grad school. Tristan remains one of my closest friends, and I cannot thank him enough for everything that we shared. I will always treasure our many memories in some of the most beautiful places in the world. Tristan also helped me to learn a lot about myself and ultimately led me in the direction of actually paying attention to what’s happening in the world. He taught me to look deeper into myself and to become the person I wanted to be instead of wishing things were different.

I’ve put this off for awhile now, but it comes time to try to thank Jenny Roizen. There aren’t words to express my gratitude to Jenny. For the first three years of grad school, Jenny was my roommate, labmate, and friend. We did everything together. I could not possibly have gotten through some of the rougher times of the past five and a half years without Jenny’s constant love and support. I have grown to really appreciate her direct candor with me about everything. To put it briefly, Jenny rocks. I’m so sad to be leaving her in the lab without me. I know that she will get through everything fine, but I wish I could be here to support her, as she has so devotedly supported me over this thesis journey.

Most people are lucky to have one friend as constant and close to their heart as Jenny is to mine. I have had the great fortune during my graduate career of having developed two such friends. Professor Dr. Jen Dionne has become a critical appendage over the years. To lose her would be like losing an arm. I am left frustrated again with the
English language for not having the appropriate words to match the quality and magnitude of Jen’s friendship. She has become like a twin sister to me, which is exciting because I never had a twin sister! I will just say to both Jen and Jenny, I love you. You are irreplaceable.

Finally, to thank the people who shaped me into who I am. Becky (Doyal) Orrock and Aimee (Dudash) Ketner have been my best friends since I can remember, and it has been awesome watching each other grow from little girls ogling at cute boys at the beach to grown women, ogling at cute boys at the beach. Sally, I am glad you moved to Virginia. It’s been nice having some extended family nearby, and I always enjoy our phone calls, surprisingly also often relating to ogling at boys at the beach! Grandma Stockdill, it has been fabulous visiting with you more often over the past ten years. I’m glad you were persistent about calling. Your support has been treasured. Grandma Vorlicek, I wish I could see you more, but I wanted to take this chance to thank you for working so hard to keep the family together over the years. I know it was challenging raising 8 kids as a single mom, and I’m amazed that you managed to do it so successfully. Teresa and Jon, thanks for all that you have done for me over the years. I have always looked up to you, and I continue to be awed by your talents as you raise your families. You have the 5 coolest kids in the world. I can’t wait to be back with you and with them. Mom and Dad, I love you both and I wish you all the happiness and adventure that you have ensured that I had the opportunity to experience. You have all contributed irreversibly to the person I have become. I cannot thank you enough.
The zoanthamine family of alkaloids has attracted the attention of synthetic chemists for over two decades, beginning with the first report of their isolation in 1984. Not only are these stereochemically dense polycyclic compounds structurally fascinating, but they also display interesting and important biological activities. Foremost among these is the potent anti-osteoporotic effect of norzoanthamine. To date, norzoanthamine remains the only member to have succumbed to total synthesis, by Miyashita and coworkers in 2004. Our studies began by targeting zoanthenol, a structurally similar natural product that possesses the key stereochemical challenges of norzoanthamine, while offering unique opportunities for strategic development as compared to the other family members.

The synthetic work described herein focuses on approaches to the tricyclic core of zoanthenol, specifically employing an approach by which the stereochemical complexity of the C ring, marked by the challenging vicinal all-carbon quaternary centers, is addressed early in the synthesis. These functionalized C ring synthons are then tethered to an aromatic A ring synthon, and methods to form the final bond of the B ring are explored. Special attention is given to the acid-mediated Friedel-Crafts cyclization approach. In addition to the acid-mediated cyclization approach, an alternative cyclization method is discussed wherein the A ring is substituted with a halogen in order to enable generation of a radical. This radical then undergoes a 1,4-addition into a fully substituted enone to close the B ring and provide the desired stereochemistry both of the two new stereocenters that are generated in the cyclization.

In these efforts, we have learned a great deal about the factors governing selectivity and reactivity in these systems. For each case, stereochemical models are discussed and key structural requirements for future investigations are outlined.
This prologue is primarily for the benefit of readers outside of the field of chemistry, who may not be familiar with the nuances of the field of total synthesis, and thus, the impact of the research described in this thesis.

Natural products are complex molecules that have been isolated from a natural source, such as a tree bark, a fungus, a bacterial species, or even a marine creature. The study of natural products synthesis is essential to the advancement of organic chemistry, as well as to society as a whole. A natural product synthesis involves looking at a structure that has been isolated from nature, and then finding a way to make it from much smaller starting materials. As such, it is an ideal platform for the discovery of new reactions because every natural product presents a unique array of bonds that have likely not been made before. In order to make some of these bonds, new chemistry must be invented. These new reactions are typically applied to related molecules of varying levels of complexity, leading to the development of a new reaction methodology. Thus, total synthesis fuels the discovery of new methodology, while new methodology simultaneously allows for the completion of total syntheses.

The broader impact of these studies is realized largely through the pharmaceutical industry. Although pharmaceutical companies invest a great deal of time and money into their own research programs, they are generally very focused on a specific goal such as finding a drug for breast cancer. This is a large enough problem on its own that the company cannot invest their own man-hours into synthesizing natural products from scratch. Thus, they turn to academic groups for key information about what bonds were the most challenging to make and what disconnections lead to the shortest and most modular synthesis of a compound. Short syntheses are important to pharmaceutical
companies because even if every step of a 30-step synthesis of a compound proceeds with 90% yield (this is not typical), the overall yield for the process is \((0.9)^{30}\) or 4%. If the company is going to conduct testing on the compound, they cannot afford to waste 96% of their original materials. Thus, it is important for academic groups to discover as many different types of reactions and ways to disconnect natural products as possible. It is also important to have a modular synthesis, so that analog compounds can be made and tested. In many cases, the best pharmaceutical agents are modified versions of natural products. Natural products offer the great advantage of having already been compatible with at least one living system, the one from which they were isolated. If that creature was able to survive with this compound inside it, it is more likely that a human will be able to tolerate the compound than for a molecule that has been 100% designed. Some important drugs that are natural products or derivatives include the antibiotics penicillin and vancomycin, contraceptives \((+)-norgestrel\) and \(17\alpha\)-ethynylestradiol, the anti-inflammatory agent indomethacin, and the ovarian, breast, and small lung cancer drug paclitaxel (taxol).

The research presented herein centers around the synthesis of a marine alkaloid, zoanthenol, isolated off the coast of the Canary Islands from polyps of the genus Zoanthus. A number of very similar compounds were also isolated from the zoanthids, and they comprise a family of natural products called the zoanthamines. As a family, the zoanthamines offer a range of biological activities including inhibition of inflammation in mouse ears, cytotoxicity against murine leukemia cells, broad-spectrum antibacterial activity, and activity against human platelet aggregation. Perhaps the most exciting biological activity is the excellent anti-osteoporotic activity demonstrated by norzoanthamine. In ovarioectomized mice, a good model for post-menopausal osteoporosis, treatment with norzoanthamine hydrochloride prevented the loss of bone mass and strength. Additionally, bone strength can be restored in ovarioectomized mice
by treatment with norzoanthamine hydrochloride without any observed uterine atrophy, a side effect of treatment with 17β-estradiol, the current standard in this type of therapy. This difference points to the possibility of a different mechanism of action than estrogen therapy, making the zoanthamines an important family of natural products to target for synthesis.
TABLE OF CONTENTS

Dedication ............................................................................................................................................ iii
Acknowledgements .............................................................................................................................. ix
Abstract ................................................................................................................................................ xi
Prologue ............................................................................................................................................... xii
Table of Contents............................................................................................................................... xv
List of Figures ........................................................................................................................................ xx
List of Schemes .................................................................................................................................... xxxiii
List of Tables ......................................................................................................................................... xl
List of Abbreviations ............................................................................................................................ xliii

CHAPTER 1: THE BIOLOGY AND CHEMISTRY OF THE ZOANTHAMINE ALKALOIDS .............................. 1
1.1.1 Introduction ............................................................................................................................... 1
1.2 The Zoanthamine Natural Products ............................................................................................ 3
1.2.1 Isolation and Structural Characterization of the Zoanthamine Natural Products ................. 3
1.2.2 Biosynthesis of the Zoanthamine Natural Products ............................................................... 6
1.2.3 Reactivity Studies of Norzoanthamine .................................................................................. 11
1.3 Biological Activities of Zoanthamine Alkaloids ........................................................................ 13
1.3.1 Anti-Osteoporotic Activity .................................................................................................... 13
1.3.2 Miscellaneous Biological Activities ...................................................................................... 15
1.4 Synthetic Approaches Toward the Zoanthamine Natural Products ......................................... 17
1.4.1 General Remarks .................................................................................................................. 17
1.4.2 Miyashita’s Synthesis of Norzoanthamine ......................................................................... 18
1.4.3 Tanner’s Diels-Alder Approach to the Zoanthamine ABC Ring System .......................... 22
CHAPTER 1: UEMURA'S APPROACH TO THE NORZOANTHAMINE ABC RING SYSTEM

1.4.4 Uemura’s Approach to the Norzoanthamine ABC Ring System ............................................. 28

1.4.5 Williams’s Approach to the Norzoanthamine AB and EFG Ring Systems ......................... 28

1.4.6 Theodorakis’s Annulation Approach to the Norzoanthamine ABC Ring System ....................... 31

1.4.7 Kobayashi’s Synthesis of the Heterocyclic CDEFG Zoanthamine Ring System ......................... 33

1.4.8 Hirama’s Strategy for the Zoanthenol ABC Ring System ....................................................... 34

1.5.1 Summary and Outlook ........................................................................................................... 38

REFERENCES .................................................................................................................................... 40

CHAPTER 2: EARLY EFFORTS TOWARD THE SYNTHESIS OF ZOANTHENOL ................................. 43

2.1.1 Introduction and Retrosynthetic Analysis .................................................................................. 43

2.2.1 Synthesis of the A Ring Synthon .............................................................................................. 45

2.2.2 Synthesis of the C Ring Synthon .............................................................................................. 45

2.2.3 Synthesis of the Tricyclic Core of Zoanthenol ....................................................................... 47

2.3.1 Enantioselective Synthesis of the DEFG Synthon ................................................................. 53

2.4.1 Summary of Early Synthetic Work ......................................................................................... 55

2.5.1 Materials and Methods .......................................................................................................... 56

2.5.2 Preparation of Compounds .................................................................................................... 58

REFERENCES .................................................................................................................................... 85

Synthetic Summary .......................................................................................................................... 89

APPENDIX A: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: EARLY EFFORTS

TOWARD THE SYNTHESIS OF ZOANTHENOL .............................................................................. 92

CHAPTER 3: ACID-MEDIATED CYCLIZATION APPROACHES TO THE DENSELY

SUBSTITUTED CARBOCYCLIC CORE OF ZOANTHENOL .......................................................... 181
3.1.1 Revised Retrosynthetic Analysis

3.2 Toward a Vicinal Quaternary Center-Containing C Ring Synthon

3.2.1 Synthesis and Desymmetrization of a meso-Anhydride

3.2.2 Elaboration of the Half-Ester

3.3 Toward a Lactone-Derived C Ring Synthon

3.3.1 Toward a Lactone-Derived C Ring Synthon

3.3.2 Acid-Mediated Cyclizations of Lactone-Derived A–C Ring Systems

3.4 Toward a Lactone-Derived C Ring Synthon

3.4.1 Functionalization of Allylic Alcohol

3.5 Toward a 7-Membered Acetal-Derived C Ring

3.5.1 Toward a 7-Membered Acetal-Derived C Ring

3.5.2 Acid-Mediated Cyclization of the 7-Membered Acetal Substrate

3.6 Toward a Lactone-Derived C Ring Synthon

3.6.1 Synthesis of a Homologated C Ring Synthon

3.6.2 Acid-Mediated Cyclizations of the Homologated A–C Ring System

3.7 Toward a Lactone-Derived C Ring Synthon

3.7.1 Modification of the Homologated A–C Ring System

3.7.2 Acid-Mediated Cyclizations of Carboxylic Acid-Derived A–C Ring Systems

3.8 Mechanistic Hypotheses

3.8.1 Mechanistic Hypotheses

3.8.2 Mechanistic Summary and Substrate Requirements

3.9 Summary of Brønsted Acid Cyclization Efforts

3.10 Materials and Methods

3.10.1 Materials and Methods

3.10.2 Preparation of Compounds

References

Summary Schemes

APPENDIX B: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: ACID-MEDIATED CYCLIZATION APPROACHES TO THE DENSELY SUBSTITUTED CARBOCYCLIC CORE OF ZOANTHENOL
CHAPTER 4: RADICAL CYCLIZATION APPROACHES TOWARD THE TRICYCLIC CORE OF ZOANTHENOL

4.1.1 Introduction .................................................................................................................. 366

4.2.1 Synthesis and Cyclization of a Lactone-Derived Precursor .......................................... 368

4.3.1 Synthesis and Cyclization of a Homologated Nitrile-Derived Cyclization Precursor ................................................................................................................................. 370

4.4.1 Synthesis and Cyclization of a Homologated Ester-Derived Cyclization Precursor ................................................................................................................................. 371

4.5.1 Synthesis and Cyclization of a 7-Membered Acetal-Derived Cyclization Precursor ................................................................................................................................. 372

4.6.1 Substrate Requirements and Limits of System .................................................................. 373

4.7.1 Summary .......................................................................................................................... 376

4.8.1 Materials and Methods .................................................................................................. 377

4.8.2 Preparation of Compounds ............................................................................................ 378

References .................................................................................................................................. 389

Summary Schemes .................................................................................................................... 390

APPENDIX C: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: RADICAL CYCLIZATION APPROACHES TOWARD THE TRICYCLIC CORE OF ZOANTHENOL ........................................................................... 392

APPENDIX D: CURRENT AND FUTURE INVESTIGATIONS TOWARD ZOANTHENOL ............... 417

D.1 Introduction ....................................................................................................................... 417

D.2 Proposed Methods for the Utilization of Tricycle 192 ...................................................... 417

D.3.1 Development and Cyclization of a 6-Membered Acetal-Derived A–C Ring System with Inverted C(10) Stereochemistry ......................................................................................... 419

D.3.2 Advancement of Cyclopentylidene-Derived C Ring Synthon for
Acid-Mediated Cyclization .............................................................................................................. 421

D.3.3 Advancement of Cyclopentylidene-Derived C Ring for Radical Cyclization .......... 422

D.4.1 Alternative Approaches to the Tricyclic Core of Zoanthanol .................................. 423

D.4.2 Allylation/Diels-Alder Approach ..................................................................................... 424

D.4.3 α-Arylation Approach .................................................................................................... 427

D.5.1 Precedence for Planned Late-Stage Side Chain Couplings .................................... 429

D.5.2 Alkyne Addition into Enantiopure Lactam Synthon .................................................... 430

D.5.3 Synthesis of a Horner-Wadsworth-Emmons Reagent for Side Chain

     Synthesis .............................................................................................................................. 431

D.6.1 Summary ....................................................................................................................... 431

D.7.1 Materials and Methods .................................................................................................. 432

D.7.2 Preparation of Compounds ............................................................................................ 433

References .................................................................................................................................. 454

APPENDIX E: SPECTRA AND X-RAY CRYSTALLOGRAPHIC DATA: CURRENT AND FUTURE

 INVESTIGATIONS TOWARD ZOANTHENOL .............................................................................. 456

Comprehensive Bibliography ..................................................................................................... 509

Notebook Cross-references ....................................................................................................... 518

About the Author ....................................................................................................................... 527
# List of Figures

## Chapter 1

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1</td>
<td>Representative zoanthids</td>
<td>1</td>
</tr>
<tr>
<td>1.1.2</td>
<td>Natural products isolated from zoanthids</td>
<td>3</td>
</tr>
<tr>
<td>1.2.1</td>
<td>Zoanthamine natural products isolated by Rao</td>
<td>4</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Zoanthamine natural products isolated by Uemura and Clardy</td>
<td>5</td>
</tr>
<tr>
<td>1.2.3</td>
<td>Zoanthamine natural products isolated by Norte</td>
<td>6</td>
</tr>
<tr>
<td>1.3.1</td>
<td>IC$_{50}$ values for the inhibition of IL-6 production in Uemura’s SAR study</td>
<td>15</td>
</tr>
<tr>
<td>1.3.2</td>
<td>IC$_{50}$ values for the inhibition of IL-6 dependent cell growth</td>
<td>15</td>
</tr>
<tr>
<td>1.4.1</td>
<td>Miyashita’s retrosynthetic analysis of norzoanthamine</td>
<td>18</td>
</tr>
<tr>
<td>1.4.2</td>
<td>Tanner’s retrosynthetic analysis of zoanthamine</td>
<td>22</td>
</tr>
<tr>
<td>1.4.3</td>
<td>Uemura’s retrosynthetic analysis of norzoanthamine</td>
<td>28</td>
</tr>
<tr>
<td>1.4.4</td>
<td>Williams’s retrosynthetic analysis of norzoanthamine</td>
<td>29</td>
</tr>
<tr>
<td>1.4.5</td>
<td>Theodorakis’s retrosynthetic analysis of norzoanthamine</td>
<td>31</td>
</tr>
<tr>
<td>1.4.6</td>
<td>Hirama’s retrosynthetic analysis of zoanthenol</td>
<td>34</td>
</tr>
</tbody>
</table>

## Appendix A

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound 172</td>
<td>93</td>
</tr>
<tr>
<td>A.2</td>
<td>Infrared spectrum (thin film/NaCl) of compound 172</td>
<td>94</td>
</tr>
<tr>
<td>A.3</td>
<td>$^{13}$C NMR (75 MHz, CDCl$_3$) of compound 172</td>
<td>94</td>
</tr>
<tr>
<td>A.4</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound 174</td>
<td>95</td>
</tr>
<tr>
<td>A.5</td>
<td>Infrared spectrum (thin film/NaCl) of compound 174</td>
<td>96</td>
</tr>
<tr>
<td>A.6</td>
<td>$^{13}$C NMR (75 MHz, CDCl$_3$) of compound 174</td>
<td>96</td>
</tr>
</tbody>
</table>
Figure A.7  $^1$H NMR (300 MHz, CDCl$_3$) of compound 173 .................................. 97
Figure A.8  Infrared spectrum (thin film/NaCl) of compound 173 ......................... 98
Figure A.9  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 173 .......................... 98
Figure A.10 $^1$H NMR (300 MHz, CDCl$_3$) of compound 175 .......................... 99
Figure A.11 Infrared spectrum (thin film/NaCl) of compound 175 ...................... 100
Figure A.12 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 175 .......................... 100
Figure A.13 $^1$H NMR (300 MHz, CDCl$_3$) of compound 168 .......................... 101
Figure A.14 Infrared spectrum (thin film/NaCl) of compound 168 ...................... 102
Figure A.15 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 168 .......................... 102
Figure A.16 $^1$H NMR (300 MHz, CDCl$_3$) of compound (+)-177 ....................... 103
Figure A.17 Infrared spectrum (thin film/NaCl) of compound (+)-177 .......... 104
Figure A.18 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound (+)-177 ....................... 104
Figure A.19 $^1$H NMR (300 MHz, CDCl$_3$) of compound (−)-177 ...................... 105
Figure A.20 Infrared spectrum (thin film/NaCl) of compound (−)-177 ........ 106
Figure A.21 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound (−)-177 ...................... 106
Figure A.22 $^1$H NMR (300 MHz, CDCl$_3$) of compound 178 .......................... 107
Figure A.23 Infrared spectrum (thin film/NaCl) of compound 178 ................. 108
Figure A.24 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 178 .......................... 108
Figure A.25 $^1$H NMR (300 MHz, CDCl$_3$) of compound 169 .......................... 109
Figure A.26 Infrared spectrum (thin film/NaCl) of compound 169 ................. 110
Figure A.27 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 169 .......................... 110
Figure A.28 $^1$H NMR (300 MHz, CDCl$_3$) of compound (−)-170 ...................... 111
Figure A.29 Infrared spectrum (thin film/NaCl) of compound (−)-170 ........ 112
Figure A.30 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound (−)-170 ...................... 112
Figure A.31 $^1$H NMR (300 MHz, CDCl$_3$) of compound (+)-180 .................... 113
Figure A.32 Infrared spectrum (thin film/NaCl) of compound (+)-180 .......... 114
Figure A.33  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound (+)$_{180}$ ................................ 114
Figure A.34  $^1$H NMR (300 MHz, CDCl$_3$) of compound 183 ........................................ 115
Figure A.35  Infrared spectrum (thin film/NaCl) of compound 183 .............................. 116
Figure A.36  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 183 ........................................ 116
Figure A.37  $^1$H NMR (300 MHz, CDCl$_3$) of compound 184 ........................................ 117
Figure A.38  Infrared spectrum (thin film/NaCl) of compound 184 ............................. 118
Figure A.39  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 184 ........................................ 118
Figure A.40  $^1$H NMR (300 MHz, CDCl$_3$) of compound 187 ........................................ 119
Figure A.41  Infrared spectrum (thin film/NaCl) of compound 187 ............................. 120
Figure A.42  $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) of compound 187 ..................................... 120
Figure A.43  $^1$H NMR (500 MHz, CDCl$_3$) of compound 188 ........................................ 121
Figure A.44  Infrared spectrum (thin film/NaCl) of compound 188 ............................. 122
Figure A.45  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 188 ..................................... 122
Figure A.46  $^1$H NMR (300 MHz, CDCl$_3$) of compound 189 ........................................ 123
Figure A.47  Infrared spectrum (thin film/NaCl) of compound 189 ............................. 124
Figure A.48  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 189 ..................................... 124
Figure A.49  $^1$H NMR (300 MHz, CDCl$_3$) of compound 191 ....................................... 125
Figure A.50  Infrared spectrum (thin film/NaCl) of compound 191 ............................. 126
Figure A.51  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 191 ..................................... 126
Figure A.52  $^1$H NMR (300 MHz, CDCl$_3$) of compound 192 ....................................... 127
Figure A.53  Infrared spectrum (thin film/NaCl) of compound 192 ............................. 128
Figure A.54  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 192 ..................................... 128
Figure A.55  $^1$H NMR (500 MHz, C$_6$D$_6$) of compound 193 ...................................... 129
Figure A.56  Infrared spectrum (thin film/NaCl) of compound 193 ............................. 130
Figure A.57  $^{13}$C NMR (125 MHz, C$_6$D$_6$) of compound 193 .................................... 130
Figure A.58  $^1$H NMR (500 MHz, CDCl$_3$) of compound 194 ...................................... 131
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.59</td>
<td>Infrared spectrum (thin film/NaCl) of compound 194</td>
<td>132</td>
</tr>
<tr>
<td>A.60</td>
<td>$^1$C NMR (125 MHz, CDCl$_3$) of compound 194</td>
<td>132</td>
</tr>
<tr>
<td>A.61</td>
<td>$^1$H NMR (500 MHz, CDCl$_3$) of compound 195</td>
<td>133</td>
</tr>
<tr>
<td>A.62</td>
<td>Infrared spectrum (thin film/NaCl) of compound 195</td>
<td>134</td>
</tr>
<tr>
<td>A.63</td>
<td>$^1$C NMR (125 MHz, CDCl$_3$) of compound 195</td>
<td>134</td>
</tr>
<tr>
<td>A.64</td>
<td>$^1$H NMR (500 MHz, CDCl$_3$) of compound 196</td>
<td>135</td>
</tr>
<tr>
<td>A.65</td>
<td>Infrared spectrum (thin film/NaCl) of compound 196</td>
<td>136</td>
</tr>
<tr>
<td>A.66</td>
<td>$^1$C NMR (125 MHz, CDCl$_3$) of compound 196</td>
<td>136</td>
</tr>
<tr>
<td>A.67</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound (–)-210</td>
<td>137</td>
</tr>
<tr>
<td>A.68</td>
<td>Infrared spectrum (thin film/NaCl) of compound (–)-210</td>
<td>138</td>
</tr>
<tr>
<td>A.69</td>
<td>$^1$C NMR (75 MHz, CDCl$_3$) of compound (–)-210</td>
<td>138</td>
</tr>
<tr>
<td>A.70</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound (–)-211</td>
<td>139</td>
</tr>
<tr>
<td>A.71</td>
<td>Infrared spectrum (thin film/NaCl) of compound (–)-211</td>
<td>140</td>
</tr>
<tr>
<td>A.72</td>
<td>$^1$C NMR (75 MHz, CDCl$_3$) of compound (–)-211</td>
<td>140</td>
</tr>
<tr>
<td>A.73</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound (–)-212</td>
<td>141</td>
</tr>
<tr>
<td>A.74</td>
<td>Infrared spectrum (thin film/NaCl) of compound (–)-212</td>
<td>142</td>
</tr>
<tr>
<td>A.75</td>
<td>$^1$C NMR (75 MHz, CDCl$_3$) of compound (–)-212</td>
<td>142</td>
</tr>
<tr>
<td>A.76</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound 213</td>
<td>143</td>
</tr>
<tr>
<td>A.77</td>
<td>Infrared spectrum (thin film/NaCl) of compound 213</td>
<td>144</td>
</tr>
<tr>
<td>A.78</td>
<td>$^1$C NMR (75 MHz, CDCl$_3$) of compound (–)-213</td>
<td>144</td>
</tr>
<tr>
<td>A.79</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound 214</td>
<td>145</td>
</tr>
<tr>
<td>A.80</td>
<td>Infrared spectrum (thin film/NaCl) of compound 214</td>
<td>146</td>
</tr>
<tr>
<td>A.81</td>
<td>$^1$C NMR (75 MHz, CDCl$_3$) of compound 214</td>
<td>146</td>
</tr>
<tr>
<td>A.82</td>
<td>$^1$H NMR (300 MHz, CDCl$_3$) of compound 215</td>
<td>147</td>
</tr>
<tr>
<td>A.83</td>
<td>Infrared spectrum (thin film/NaCl) of compound 215</td>
<td>148</td>
</tr>
<tr>
<td>A.84</td>
<td>$^1$C NMR (75 MHz, CDCl$_3$) of compound 215</td>
<td>148</td>
</tr>
</tbody>
</table>
Figure A.85  
^1H NMR (300 MHz, CDCl₃) of compound 215a.......................... 149

Figure A.86  
Infrared spectrum (thin film/NaCl) of compound 215a................. 150

Figure A.87  
^13C NMR (75 MHz, CDCl₃) of compound 215a.......................... 150

Figure A.88  
^1H NMR (300 MHz, CDCl₃) of compound 203............................ 151

Figure A.89  
Infrared spectrum (thin film/NaCl) of compound 203................. 152

Figure A.90  
^13C NMR (75 MHz, CDCl₃) of compound 203............................ 152

Figure A.91  
^1H NMR (500 MHz, CDCl₃) of compound 168............................ 153

Figure A.92  
Infrared spectrum (thin film/NaCl) of compound 168.................. 154

Figure A.93  
^13C NMR (125 MHz, CDCl₃) of compound 168............................ 154

Figure A.94  
Representation of Lactone 184............................................ 155

Figure A.95  
Representation of Acid 187·CHCl₃ ........................................ 164

Figure A.96  
Representation of Diketone 196............................................ 173

CHAPTER 3

Figure 3.2.1  
Known meso-anhydride desymmetrization substrates.................. 184

Figure 3.8.1  
Requirements for future acid cyclization substrates.................. 202

APPENDIX B

Figure B.1  
^1H NMR (500 MHz, CDCl₃) of compound 225........................... 241

Figure B.2  
Infrared spectrum (thin film/NaCl) of compound 225.................. 242

Figure B.3  
^13C NMR (125 MHz, CDCl₃) of compound 225........................... 242

Figure B.4  
^1H NMR (500 MHz, CDCl₃) of compound 226........................... 243

Figure B.5  
Infrared spectrum (thin film/NaCl) of compound 226.................. 244

Figure B.6  
^13C NMR (125 MHz, CDCl₃) of compound 226........................... 244

Figure B.7  
^1H NMR (500 MHz, CDCl₃) of compound 242........................... 245

Figure B.8  
Infrared spectrum (thin film/NaCl) of compound 242.................. 246

Figure B.9  
^13C NMR (125 MHz, CDCl₃) of compound 242........................... 246
Figure B.10  $^1$H NMR (300 MHz, C$_6$D$_6$) of compound 247

Figure B.11  Infrared spectrum (thin film/NaCl) of compound 247

Figure B.12  $^{13}$C NMR (75 MHz, C$_6$D$_6$) of compound 247

Figure B.13  $^1$H NMR (500 MHz, CDCl$_3$) of compound 247a

Figure B.14  Infrared spectrum (thin film/NaCl) of compound 247a

Figure B.15  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 247a

Figure B.16  $^1$H NMR (500 MHz, CDCl$_3$) of compound 248

Figure B.17  Infrared spectrum (thin film/NaCl) of compound 248

Figure B.18  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 248

Figure B.19  $^1$H NMR (300 MHz, CDCl$_3$) of compound 250

Figure B.20  Infrared spectrum (thin film/NaCl) of compound 250

Figure B.21  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 250

Figure B.22  $^1$H NMR (300 MHz, CDCl$_3$) of compound 251

Figure B.23  Infrared spectrum (thin film/NaCl) of compound 251

Figure B.24  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 251

Figure B.25  $^1$H NMR (300 MHz, CDCl$_3$) of compound 251a

Figure B.26  Infrared spectrum (thin film/NaCl) of compound 251a

Figure B.27  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 252

Figure B.28  $^1$H NMR (300 MHz, CDCl$_3$) of compound 252

Figure B.29  Infrared spectrum (thin film/NaCl) of compound 252

Figure B.30  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 252

Figure B.31  $^1$H NMR (300 MHz, CDCl$_3$) of compound 253

Figure B.32  Infrared spectrum (thin film/NaCl) of compound 253

Figure B.33  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 253

Figure B.34  $^1$H NMR (300 MHz, CDCl$_3$) of compound 255

Figure B.35  Infrared spectrum (thin film/NaCl) of compound 255
Figure B.36 $^{13}$C NMR (75 MHz, 255) of compound 255 ................................ 264
Figure B.37 $^1$H NMR (500 MHz, CDCl$_3$) of compound 256 ................... 265
Figure B.38 Infrared spectrum (thin film/NaCl) of compound 256 .......... 266
Figure B.39 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 256 ................. 266
Figure B.40 $^1$H NMR (500 MHz, CDCl$_3$) of compound 257 ............... 267
Figure B.41 Infrared spectrum (thin film/NaCl) of compound 257 .......... 268
Figure B.42 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 257 ............... 268
Figure B.43 $^1$H NMR (300 MHz, CDCl$_3$) of compound 258 ................ 269
Figure B.44 Infrared spectrum (thin film/NaCl) of compound 258 .......... 270
Figure B.45 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 258 ............... 270
Figure B.46 $^1$H NMR (300 MHz, CDCl$_3$) of compound 259 ................ 271
Figure B.47 Infrared spectrum (thin film/NaCl) of compound 259 .......... 272
Figure B.48 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 259 ............... 272
Figure B.49 $^1$H NMR (300 MHz, CDCl$_3$) of compound 260 ................ 273
Figure B.50 Infrared spectrum (thin film/NaCl) of compound 260 .......... 274
Figure B.51 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 260 ................ 274
Figure B.52 $^1$H NMR (300 MHz, CDCl$_3$) of compound 261 ................ 275
Figure B.53 Infrared spectrum (thin film/NaCl) of compound 261 .......... 276
Figure B.54 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 261 ................ 276
Figure B.55 $^1$H NMR (300 MHz, CDCl$_3$) of compound 262a ............... 277
Figure B.56 Infrared spectrum (thin film/NaCl) of compound 262a .......... 278
Figure B.57 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 262a ............... 278
Figure B.58 $^1$H NMR (300 MHz, CDCl$_3$) of compound 262b ............... 279
Figure B.59 Infrared spectrum (thin film/NaCl) of compound 262b .......... 280
Figure B.60 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 262b ............... 280
Figure B.61 $^1$H NMR (300 MHz, C$_6$D$_6$) of compound 263 ................. 281
Figure B.88  $^1$H NMR (300 MHz, CDCl$_3$) of compound 278 ......................... 299
Figure B.89  Infrared spectrum (thin film/NaCl) of compound 278 .................. 300
Figure B.90  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 278 .................... 300
Figure B.91  $^1$H NMR (300 MHz, CDCl$_3$) of compound 279 .................... 301
Figure B.92  Infrared spectrum (thin film/NaCl) of compound 279 ............... 302
Figure B.93  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 279 .................... 302
Figure B.94  $^1$H NMR (500 MHz, CDCl$_3$) of compound 280 .................... 303
Figure B.95  Infrared spectrum (thin film/NaCl) of compound 280 ............... 304
Figure B.96  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 280 .................... 304
Figure B.97  $^1$H NMR (500 MHz, CDCl$_3$) of compound 281a .................... 305
Figure B.98  Infrared spectrum (thin film/NaCl) of compound 281a ............... 306
Figure B.99  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 281a .................... 306
Figure B.100 $^1$H NMR (500 MHz, CDCl$_3$) of compound 281b .................... 307
Figure B.101 Infrared spectrum (thin film/NaCl) of compound 281b ............... 308
Figure B.102 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 281b .................... 308
Figure B.103 $^1$H NMR (300 MHz, CDCl$_3$) of compound 282 .................... 309
Figure B.104 Infrared spectrum (thin film/NaCl) of compound 282 ............... 310
Figure B.105 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 282 .................... 310
Figure B.106 $^1$H NMR (300 MHz, CDCl$_3$) of compound 269 .................... 311
Figure B.107 Infrared spectrum (thin film/NaCl) of compound 269 ............... 312
Figure B.108 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 269 .................... 312
Figure B.109 $^1$H NMR (300 MHz, CDCl$_3$) of compound 283 .................... 313
Figure B.110 Infrared spectrum (thin film/NaCl) of compound 283 ............... 314
Figure B.111 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 283 .................... 314
Figure B.112 Representation of Allylic Alcohol 248 ................................. 315
Figure B.113 Representation of Allylic Alcohol 253 ................................. 323
Figure B.114  Representation of Bisacetoxyacetal 256 ................................ 338
Figure B.115  Representation of Tetracycle 269 ........................................ 347

APPENDIX C

Figure C.1  $^1$H NMR (500 MHz, CDCl$_3$) of compound 255a ...................... 393
Figure C.2  Infrared spectrum (thin film/NaCl) of compound 255a ........... 394
Figure C.3  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 255a ................. 394
Figure C.4  $^1$H NMR (500 MHz, CDCl$_3$) of compound 255b ................... 395
Figure C.5  Infrared spectrum (thin film/NaCl) of compound 255b .......... 396
Figure C.6  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 255b ................. 396
Figure C.7  $^1$H NMR (500 MHz, CDCl$_3$) of compound 315 ...................... 397
Figure C.8  Infrared spectrum (thin film/NaCl) of compound 315 .............. 398
Figure C.9  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 315 ...................... 398
Figure C.10 $^1$H NMR (500 MHz, CDCl$_3$) of compound 317 ....................... 399
Figure C.11 Infrared spectrum (thin film/NaCl) of compound 317 ............. 400
Figure C.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 317 ...................... 400
Figure C.13 $^1$H NMR (300 MHz, CDCl$_3$) of compound 320 ....................... 401
Figure C.14 Infrared spectrum (thin film/NaCl) of compound 320 ............. 402
Figure C.15 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 320 ....................... 402
Figure C.16 $^1$H NMR (300 MHz, CDCl$_3$) of compound 322 ....................... 403
Figure C.17 Infrared spectrum (thin film/NaCl) of compound 322 ............. 404
Figure C.18 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 322 ....................... 404
Figure C.19 $^1$H NMR (500 MHz, CDCl$_3$) of compound 323 ....................... 405
Figure C.20 Infrared spectrum (thin film/NaCl) of compound 323 ............. 406
Figure C.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 323 ....................... 406
Figure C.22 $^1$H NMR (500 MHz, CDCl$_3$) of compound 324 ....................... 407
### APPENDIX E

| Figure E.1  | $^1$H NMR (500 MHz, CDCl$_3$) of compound 341................................. 457 |
| Figure E.2  | Infrared spectrum (thin film/NaCl) of compound 341........................... 458 |
| Figure E.3  | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 341.............................. 458 |
| Figure E.4  | $^1$H NMR (300 MHz, CDCl$_3$) of compound 342................................. 459 |
| Figure E.5  | Infrared spectrum (thin film/NaCl) of compound 342........................... 460 |
| Figure E.6  | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 342.............................. 460 |
| Figure E.7  | $^1$H NMR (500 MHz, CDCl$_3$) of compound 343................................. 461 |
| Figure E.8  | Infrared spectrum (thin film/NaCl) of compound 343........................... 462 |
| Figure E.9  | $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 343.............................. 462 |
| Figure E.10 | $^1$H NMR (500 MHz, CDCl$_3$) of compound 344................................. 463 |
| Figure E.11 | Infrared spectrum (thin film/NaCl) of compound 344........................... 464 |
| Figure E.12 | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 344.............................. 464 |
| Figure E.13 | $^1$H NMR (500 MHz, CDCl$_3$) of compound 346................................. 465 |
| Figure E.14 | Infrared spectrum (thin film/NaCl) of compound 346........................... 466 |
| Figure E.15 | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 346.............................. 466 |
| Figure E.16 | $^1$H NMR (500 MHz, CDCl$_3$) of compound 347................................. 467 |
| Figure E.17 | Infrared spectrum (thin film/NaCl) of compound 347........................... 468 |
| Figure E.18 | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 347.............................. 468 |
| Figure E.19 | $^1$H NMR (300 MHz, CDCl$_3$) of compound 348a................................. 469 |
| Figure E.20 | Infrared spectrum (thin film/NaCl) of compound 348a.......................... 470 |
| Figure E.21 | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 348a.............................. 470 |
Figure E.22 $^1$H NMR (500 MHz, CDCl$_3$) of compound 348b ..................... 471
Figure E.23 Infrared spectrum (thin film/NaCl) of compound 348b .......... 472
Figure E.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 348b .......... 472
Figure E.25 $^1$H NMR (300 MHz, CDCl$_3$) of compound 348c .......... 473
Figure E.26 Infrared spectrum (thin film/NaCl) of compound 348c .......... 474
Figure E.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 348c .......... 474
Figure E.28 $^1$H NMR (500 MHz, CDCl$_3$) of compound 364 .......... 475
Figure E.29 Infrared spectrum (thin film/NaCl) of compound 364 .......... 476
Figure E.30 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 364 .......... 476
Figure E.31 $^1$H NMR (500 MHz, CDCl$_3$) of compound 365 .......... 477
Figure E.32 Infrared spectrum (thin film/NaCl) of compound 365 .......... 478
Figure E.33 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 365 .......... 478
Figure E.34 $^1$H NMR (500 MHz, CDCl$_3$) of compound 366 .......... 479
Figure E.35 Infrared spectrum (thin film/NaCl) of compound 366 .......... 480
Figure E.36 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 366 .......... 480
Figure E.37 $^1$H NMR (500 MHz, CDCl$_3$) of compound 368 .......... 481
Figure E.38 Infrared spectrum (thin film/NaCl) of compound 368 .......... 482
Figure E.39 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 368 .......... 482
Figure E.40 $^1$H NMR (500 MHz, CDCl$_3$) of compound 379 .......... 483
Figure E.41 Infrared spectrum (thin film/NaCl) of compound 379 .......... 484
Figure E.42 $^{13}$C NMR (XXX MHz, XX) of compound 379 .......... 484
Figure E.43 $^1$H NMR (300 MHz, CDCl$_3$) of compound 380 .......... 485
Figure E.44 Infrared spectrum (thin film/NaCl) of compound 380 .......... 486
Figure E.45 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 380 .......... 486
Figure E.46 $^1$H NMR (300 MHz, CDCl$_3$) of compound 387 .......... 487
Figure E.47 Infrared spectrum (thin film/NaCl) of compound 387 .......... 488
| Figure E.48 | $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 387 | 488 |
| Figure E.49 | $^1$H NMR (300 MHz, CDCl$_3$) of compound 388 | 489 |
| Figure E.50 | Infrared spectrum (thin film/NaCl) of compound 388 | 490 |
| Figure E.51 | $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 380 | 490 |
| Figure E.52 | $^1$H NMR (300 MHz, CDCl$_3$) of compound 389 | 491 |
| Figure E.53 | Infrared spectrum (thin film/NaCl) of compound 389 | 492 |
| Figure E.54 | $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 389 | 492 |
| Figure E.55 | $^1$H NMR (300 MHz, CDCl$_3$) of compound 391 | 493 |
| Figure E.56 | Infrared spectrum (thin film/NaCl) of compound 391 | 494 |
| Figure E.57 | $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 391 | 494 |
| Figure E.58 | $^1$H NMR (500 MHz, CDCl$_3$) of compound 392 | 495 |
| Figure E.59 | Infrared spectrum (thin film/NaCl) of compound 392 | 496 |
| Figure E.60 | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 392 | 496 |
| Figure E.61 | $^1$H NMR (500 MHz, CDCl$_3$) of compound 393 | 497 |
| Figure E.62 | Infrared spectrum (thin film/NaCl) of compound 393 | 498 |
| Figure E.63 | $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 393 | 498 |
| Figure E.64 | $^1$H NMR (300 MHz, CDCl$_3$) of compound 396 | 499 |
| Figure E.65 | Infrared spectrum (thin film/NaCl) of compound 396 | 500 |
| Figure E.66 | $^{13}$C NMR (75 MHz, 75) of compound 396 | 500 |
| Figure E.67 | Representation of Allyl ketone 366 | 501 |
LIST OF SCHEMES

CHAPTER 1

Scheme 1.2.1 Hypothetical polyketide precursor.................................7
Scheme 1.2.2 Potential mechanism for cyclization of polyketide precursor 22 ...8
Scheme 1.2.3 Proposed biosynthesis of norzoanthamine..........................9
Scheme 1.2.4 Structure of zooxanthellamine .......................................10
Scheme 1.2.5 Equilibria between lactone and enamine isomers of
norzoanthamine...........................................................................12
Scheme 1.2.6 Anomalous reduction of norzoanthamine.........................12
Scheme 1.4.1 Miyashita’s Diels-Alder construction of the ABC core........19
Scheme 1.4.2 Functionalization of the ABC core.................................20
Scheme 1.4.3 Attaching the southern sidechain...................................21
Scheme 1.4.4 The completion of norzoanthamine.................................22
Scheme 1.4.5 Tanner’s approach to a model ABC ring system...............23
Scheme 1.4.6 Model cyclizations of compounds derived from (−)-carvone....24
Scheme 1.4.7 Mechanism for formation of undesired products ..........25
Scheme 1.4.8 Tanner’s approach to the functionalized ABC ring system....26
Scheme 1.4.9 Mechanism for formation of by-product 95..........................26
Scheme 1.4.10 Diels-Alder cyclization and cycloadducts advancement........27
Scheme 1.4.11 Uemura’s approach to norzoanthamine .........................28
Scheme 1.4.12 Williams’s early efforts toward the norzoanthamine AB
rings..............................................................................................29
Scheme 1.4.13 Williams’s recent efforts toward the norzoanthamine AB
rings...............................................................................................30
Scheme 1.4.14 Williams’s synthesis of a model EFG ring system............31
### Scheme 1.4.15
Theodorakis’s approach to the ABC ring system ........................ 32

### Scheme 1.4.16
Theodorakis’s installation of the C(9) quaternary center ............ 33

### Scheme 1.4.17
Kobayashi’s sulfone approach to the CDEFG ring system .......... 34

### Scheme 1.4.18
Hirama’s Heck strategy for the zoanthenol ABC ring system ...... 35

### Scheme 1.4.19
Hirama’s alternative assembly of the B ring .......................... 36

### Scheme 1.4.20
Hirama’s installation of the C(9) methyl group ....................... 36

### Scheme 1.4.21
An alternate approach by Hirama .................................. 37

### Scheme 1.4.22
Hirama’s synthesis of the fully functionalized ABC core of zoanthenol .......................................................... 38

### CHAPTER 2

### Scheme 2.1.1
Retrosynthetic analysis of zoanthenol .................................. 44

### Scheme 2.2.1
Synthesis of the A ring synthon .......................................... 45

### Scheme 2.2.2
Racemic synthesis of the C ring synthon ............................... 46

### Scheme 2.2.3
Decarboxylative alkylation enables enantioselective synthesis ................................................................. 47

### Scheme 2.2.4
Diastereoselective Grignard addition .................................... 47

### Scheme 2.2.5
Discovery of an unusual acid-mediated cyclization .................. 48

### Scheme 2.2.6
Other substrates for cyclization .......................................... 49

### Scheme 2.2.7
A proposed mechanism for the $S_N$’ cyclization ................... 50

### Scheme 2.2.8
Deoxygenation of the A ring ............................................. 50

### Scheme 2.2.9
Refunctionalization of the C(20)-C(21) olefin ....................... 51

### Scheme 2.2.10
Plan for the elaboration of the tricyclic core ......................... 52

### Scheme 2.2.11
Attempts to enolize at C(9) .................................................. 53

### Scheme 2.3.1
Retrosynthetic analysis of the DEFG synthon ....................... 53

### Scheme 2.3.2
Jacobsen hetero-Diels-Alder cycloaddition ........................... 54
Scheme 2.3.3  Conjugate addition and Mitsunobu reaction provide key intermediate.................................................................54
Scheme 2.3.4  Conversion of the δ-lactone to the ε-lactam synthon.............55
Scheme 2.3.5  Vinlylation of the ε-lactam to access the enone synthon ........55

SUMMARY SCHEMES

Scheme S2.1  Retrosynthetic Analysis of Zoanthenol.................................89
Scheme S2.2  Synthesis of the A Ring Synthon ........................................89
Scheme S2.3  Racemic Synthesis of the C Ring Synthon .............................90
Scheme S2.4  Enantioselective Synthesis of C Ring Methyl Ketone 177 ..........90
Scheme S2.5  Fragment Coupling and Acid-Mediated Cyclization of the A
and C Rings ........................................................................90
Scheme S2.6  Deoxygenation of the A Ring and Refunctionalization of C(20) ..91
Scheme S2.7  Enantioselective Synthesis of DEFG Synthon .......................91

CHAPTER 3

Scheme 3.1.1  Revised retrosynthesis of zoanthenol ....................................182
Scheme 3.2.1  Synthesis of vicinal all-carbon quaternary centers .................183
Scheme 3.2.2  Mechanism of meso-anhydride desymmetrization by
cinchona alkaloids ................................................................183
Scheme 3.2.3  C ring functionalization: iodolactonization and
displacement ........................................................................187
Scheme 3.3.1  Synthesis of a lactone-derived C ring synthon ......................188
Scheme 3.3.2  Grignard addition to synthon 252 ........................................188
Scheme 3.3.3  Lactone-derived A–C ring system cyclizations .......................189
Scheme 3.4.1  Lactone reduction and triol differentiation .............................190
Scheme 3.5.1  Synthesis of a 7-membered acetal-derived C ring ..................191
Scheme 3.5.2 Grignard addition and oxidation to access cyclization substrates .............................................................................................................................................. 192
Scheme 3.5.3 Cyclization of allylic alcohol 265 .............................................................................................................................................................................. 192
Scheme 3.5.4 Cyclization of 7-membered acetal-derived enone substrate .......... 193
Scheme 3.6.1 Synthesis of a homologated C ring synthon .................................................. 195
Scheme 3.6.2 Fragment coupling and cyclization of the nitrile-derived A–C system ........................................................................................................................................... 195
Scheme 3.7.1 Synthesis of an acid-derived A–C ring system ........................................... 196
Scheme 3.7.2 Cyclization of carboxylic acid-derived tethered A–C ring systems ......................................................................................................................................................... 197
Scheme 3.8.1 Proposed mechanism for formation of bis-lactone 256 .............. 198
Scheme 3.8.2 Proposed mechanism for formation of acetal 270 ................. 199
Scheme 3.8.3 Proposed mechanism for formation of tetracycle 269 .......... 200

SUMMARY SCHEMES

Scheme S3.1 Revised retrosynthetic analysis ...................................................... 243
Scheme S3.2 Access to a meso anhydride ......................................................... 243
Scheme S3.2 Desymmetrization and elaboration of a meso anhydride ........ 244
Scheme S3.3 Synthesis of a lactone-derived C ring synthon ............................ 244
Scheme S3.4 Fragment coupling and cyclization of the A and lactone-derived C rings ........................................................................................................ 244
Scheme S3.5 Elaboration of lactone 248 .......................................................... 245
Scheme S3.6 Synthesis of a 7-membered acetal-derived C ring synthon ....... 245
Scheme S3.7 Fragment coupling and cyclization of the A and 7-membered acetal derived C rings ........................................................................................................ 245
Scheme S3.8 Synthesis of a homologated nitrile-derived C ring synthon ....... 246
Scheme S3.9  Fragment coupling and cyclization of the A and homologated nitrile-derived C rings .................................................................246
Scheme S3.10 Synthesis, fragment coupling, and cyclization of the A and homologated carboxylic acid-derived C rings.................................247

Chapter 4

Scheme 4.1.1 Failed methods for cyclization of tethered A–C ring systems .............................................................................................367
Scheme 4.1.2 Radical-induced cyclization of a tethered A–C ring system ......368
Scheme 4.2.1 Synthesis of lactone-derived radical cyclization precursor ..........369
Scheme 4.2.2 Attempted cyclization of lactone-derived A–C ring system ......369
Scheme 4.3.1 Synthesis of homologated nitrile-derived radical cyclization precursor .....................................................................................370
Scheme 4.3.2 Attempted cyclization of nitrile-derived A–C ring system ..........371
Scheme 4.4.1 Synthesis of homologated ester-derived radical cyclization precursor .....................................................................................371
Scheme 4.4.2 Attempted cyclization of ester-derived A–C ring system ..........372
Scheme 4.5.1 Synthesis of 7-membered acetal-derived radical cyclization precursor .....................................................................................372
Scheme 4.5.2 Cyclization of 7-membered acetal-derived A–C ring system .....373
Scheme 4.6.1 3D representations of cyclization products .................................375
Scheme 4.6.2 Structural requirements for future radical cyclization products.....................................................................................376

Summary Schemes

Scheme S4.1 Synthesis of brominated radical cyclization precursors ..........390
APPENDIX D

Scheme D.2.1 Plan for functionalization of C(9) ..............................................417
Scheme D.2.2 Deuteration to functionalize C(9) by allylation ...........................................418
Scheme D.2.3 Thermodynamic deprotonation to functionalize C(9) by acylation ...........................................418
Scheme D.3.1 Common intermediate for acid-mediated and radical cyclizations ...........................................419
Scheme D.3.2 Toward an optimal C ring synthon ...........................................420
Scheme D.3.3 Preparation of a C ring synthon with inverted C(10) stereochemistry ...........................................421
Scheme D.3.4 Acid-mediated cyclization of cyclopentylidene-derived C ring synthon ...........................................422
Scheme D.3.5 Radical cyclization of cyclopentylidene-containing precursor ...........................................422
Scheme D.3.6 Radical cyclization of C(19)-substituted cyclization precursor ...........................................423
Scheme D.4.1 Revised retrosynthesis for allylation/Diels-Alder approach ...............424
Scheme D.4.2 Palladium-catalyzed alkylation of lactone 366 ...........................................425
Scheme D.4.3 Allylation of a cyclopentylidene-containing ketone ...........................................425
Scheme D.4.4 Alternative alkylation and advancement of ketone 347 ...........................................427
Scheme D.4.5 Revised retrosynthesis for α-arylation approach ...........................................428
Scheme D.4.6 Synthesis of aryl bromide 379 ...........................................428
Scheme D.4.7 α-Arylation to form A–C ring adduct 380 ...........................................429
Scheme D.4.8  B ring closure of $\alpha$-arylation product 380 ........................................429
Scheme D.5.1  Side chain functionalization of a model ketone......................... 430
Scheme D.5.2  Horner-Wadsworth-Emmons coupling strategy..........................431
LIST OF TABLES

CHAPTER 1

Table 1.3.1  Cytotoxicity of the zoanthamine alkaloids ........................................16
Table 1.3.2  Summary of antibacterial activities ..................................................16

APPENDIX A

Table A.1  Crystal data .......................................................................................153
Table A.2  Atomic coordinates ..........................................................................155
Table A.3  Full bond distances and angles (for deposit) .......................................155
Table A.4  Anisotropic displacement parameters .................................................159
Table A.5  Hydrogen atomic coordinates ...............................................................160
Table A.6  Crystal data .......................................................................................162
Table A.7  Atomic coordinates ..........................................................................164
Table A.8  Full bond distances and angles (for deposit) .......................................165
Table A.9  Anisotropic displacement parameters .................................................167
Table A.10 Hydrogen atomic coordinates .............................................................168
Table A.11 Hydrogen bonds .................................................................................169
Table A.12 Crystal data .......................................................................................171
Table A.13 Atomic coordinates ..........................................................................173
Table A.14 Full bond distances and angles (for deposit) .......................................174
Table A.15 Anisotropic displacement parameters .................................................176
Table A.16 Hydrogen atomic coordinates .............................................................177
CHAPTER 3

Table 3.2.1  Optimized synthesis and desymmetrization of a C ring

meso-anhydride ........................................................................................................ 183

APPENDIX B

Table B.1  Crystal data ............................................................................................ 369
Table B.2  Atomic coordinates ................................................................................. 371
Table B.3  Full bond distances and angles ............................................................... 372
Table B.4  Anisotropic displacement parameters ..................................................... 373
Table B.5  Hydrogen atomic coordinates .................................................................. 374
Table B.6  Hydrogen bond distances and angles ..................................................... 375
Table B.7  Crystal data ............................................................................................ 377
Table B.8  Atomic coordinates ................................................................................. 379
Table B.9  Full bond distances and angles ............................................................... 381
Table B.10 Anisotropic displacement parameters .................................................... 386
Table B.11 Hydrogen atomic coordinates .................................................................. 388
Table B.12 Hydrogen bond distances and angles ..................................................... 390
Table B.13 Crystal data ............................................................................................ 392
Table B.14 Atomic coordinates ................................................................................. 394
Table B.15 Full bond distances and angles ............................................................... 395
Table B.16 Anisotropic displacement parameters .................................................... 397
Table B.17 Hydrogen atomic coordinates .................................................................. 398
Table B.18 Hydrogen bond distances and angles ..................................................... 399
Table B.19 Crystal data ............................................................................................ 401
Table B.20 Atomic coordinates ................................................................................. 403
Table B.21 Full bond distances and angles ............................................................... 405
Table B.22  Anisotropic displacement parameters ........................................ 409
Table B.23  Hydrogen bond distances and angles ........................................ 411

APPENDIX C

Table C.1  Crystal data ................................................................................. 454
Table C.2  Atomic coordinates ...................................................................... 456
Table C.3  Full bond distances and angles ...................................................... 458

APPENDIX E

Table E.1  Crystal data ................................................................................. 547
Table E.2  Atomic coordinates ...................................................................... 549
Table E.3  Full bond distances and angles ...................................................... 550
Table E.4  Anisotropic displacement parameters ........................................... 552
Table E.5  Hydrogen atomic coordinates ......................................................... 553
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha]_D$</td>
<td>specific rotation at wavelength of sodium D line</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>Ad</td>
<td>adamantyl</td>
</tr>
<tr>
<td>add’n</td>
<td>addition</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2’-azobis(iso-butyronitrile)</td>
</tr>
<tr>
<td>app.</td>
<td>apparent</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl group</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>B.</td>
<td>Bacillus</td>
</tr>
<tr>
<td>BBN</td>
<td>borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>BHT</td>
<td>2,6-di-tert-butyl-4-methylphenol</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>bm</td>
<td>broad multiplet</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>BOM</td>
<td>benzyloxyethyl</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>BRSM</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>bs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>BSA</td>
<td>$N,O$-bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
</tbody>
</table>
\textit{n-Bu} \quad n\text{-butyl}
\textit{t-Bu} \quad \textit{tert}\text{-butyl}
\text{Bz} \quad \text{benzoyl}
\text{c} \quad \text{concentration for optical rotation measurement}
\text{\textsuperscript{13}C} \quad \text{carbon 13, isotope}
\text{/C} \quad \text{supported on activated carbon}
\text{oC} \quad \text{degrees Celsius}
\text{cat.} \quad \text{catalytic}
\text{calc’d} \quad \text{calculated}
\text{CAM} \quad \text{ceric ammonium molybdate stain}
\text{CAN} \quad \text{ammonium cerium(IV) nitrate}
\text{Cbz} \quad \text{benzyloxycarbonyl}
\text{CCDC} \quad \text{Cambridge Crystallographic Data Centre}
\text{CDI} \quad 1,1’\text{-carbonyldiimidazole}
\text{c-Hex} \quad \text{cyclohexyl}
\text{comb.} \quad \text{combined}
\text{comp.} \quad \text{complex}
\text{CSA} \quad \text{camphorsulfonic acid}
\text{conv} \quad \text{conversion}
\text{COSY} \quad \text{correlation spectroscopy}
\text{Cy} \quad \text{cyclohexyl}
\text{d} \quad \text{doublet, deuterium, diameter, or day(s)}
\Delta \quad \text{heat}
\delta \quad \text{chemical shift in parts per million}
\text{DA} \quad \text{Diels-Alder}
\text{dba} \quad \text{dibenzylideneacetone}
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane or methylene chloride</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-p-benzoquinone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>decomp.</td>
<td>decomposes</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIOP</td>
<td>2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>DIPA</td>
<td>diisopropyl amine</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>dmdba</td>
<td>3,5,3',5'-dimethoxydibenzylideneacetone</td>
</tr>
<tr>
<td>DMDO</td>
<td>dimethyldioxirane</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-dimethyl propylene urea</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethylsulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>dppb</td>
<td>1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>DPPE</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
</tbody>
</table>
dppp 1,3-bis(diphenylphosphino)propane
dr diastereomeric ratio
D.-S. Dean-Stark conditions
ee enantiomeric excess
E entgegen olefin geometry
E. Escherichia
eI electrospray ionization
equiv equivalent(s)
Et ethyl
FAB fast atom bombardment
g gram
GC gas chromatography
Grubbs II Grubbs second-generation metathesis catalyst
[H] reduction
h hour(s) or height
hv light
¹H proton
³H tritium
HMBC heteronuclear multiple bond correlation
HMDS hexamethyldisilazide or hexamethyldisilizane
HMPA hexamethylphosphoramide
HPLC high-performance liquid chromatography
HRMS high-resolution mass spectroscopy
HSQC heteronuclear single quantum coherence
Hz hertz
η^n eta; n = number of atoms coordinated to metal
i iso
IBX 2-iodoxybenzoic acid
IC\textsubscript{50} concentration required for 50\% growth inhibition
IL interleukin
IMDA intramolecular Diels-Alder
imid. imidazole
Imid. imidazole
IR infrared spectroscopy
\(J\) coupling constant
k kilo
\(k_n\) rate constant, n refers to various reactions, negative n indicates reverse reaction
kcal kilocalories
KHMDS potassium hexamethyldisilazide
L liter
\(\lambda\) wavelength
LAH lithium aluminum hydride
LDA lithium diisopropylamide
LD\textsubscript{50} Lethal Dosage to kill 50\% of test population
LiHMDS lithium hexamethyldisilazide
LITA lithium tantalate
lut. lutidine
\(m\) meta
\(m\) multiplet, meter, or milli
\(\mu\) micro
M mega, metal, or molar
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>m-CPBA</td>
<td><em>meta</em>-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>(R,R)-Me-DUPHOS</td>
<td>(-)-1,2-Bis((2R,5R)-2,5-dimethylphospholano)benzene</td>
</tr>
<tr>
<td>MEK</td>
<td>methyl ethyl ketone</td>
</tr>
<tr>
<td>MH-60</td>
<td>mouse myelohybridoma cells</td>
</tr>
<tr>
<td>MIC</td>
<td>minimal inhibitory concentration</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>mol%</td>
<td>percentage used based on moles</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>(R)-MOP</td>
<td>(R)-(+) -2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl</td>
</tr>
<tr>
<td>mp or m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>M.S.</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>MTPA</td>
<td>α-methoxy-α-(trifluoromethyl)phenylacetic acid</td>
</tr>
<tr>
<td>MVK</td>
<td>methyl vinyl ketone</td>
</tr>
<tr>
<td>N</td>
<td>normal</td>
</tr>
<tr>
<td>n</td>
<td>normal</td>
</tr>
<tr>
<td>n</td>
<td>nano</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidinone</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>NOESY</td>
<td>2D nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>NR</td>
<td>no reaction</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>[O]</td>
<td>oxidation</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>PG</td>
<td>prostoglandin</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pH</td>
<td>hydrogen ion concentration in aqueous solution</td>
</tr>
<tr>
<td>PhH</td>
<td>benzene</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
</tr>
<tr>
<td>PHOX</td>
<td>phosphinooxazoline</td>
</tr>
<tr>
<td>Phth</td>
<td>phthalamidyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMA</td>
<td>phorbol myristate acetate</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PMBM</td>
<td>p-methoxybenzyloxymethyl</td>
</tr>
<tr>
<td>p.o.</td>
<td>administered orally</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
<tr>
<td>Py, py or Pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
</tbody>
</table>
QUINAP \((R)-(+)-1-(2\text{-diphenylphosphino-1-naphthyl})\text{isoquinoline}\)

R alkyl group

\(R\) rectus (configurational)

Rearr. Rearrangement

Red-Al sodium bis(2-methoxyethoxy)aluminum hydride

\(R_f\) retention factor

RNA ribonucleic acid

ROESY rotational nuclear Overhauser effect spectroscopy

s singlet

\(S\) sinister (configurational)

\(S.\) \(Salmonella\) or \(Staphylococcus\)

SAE Sharpless asymmetric epoxidation

SAR structure activity relationship

sat. saturated

sept. septet

\(S_N^1\) allylic nucleophilic substitution

\(S_N^1\) unimolecular nucleophilic substitution

\(S_N^2\) bimolecular nucleophilic substitution

\(sp.\) \(species\)

stoich. stoichiometric

t triplet

\(t\) \text{tertiary}

\(t_{1/2}\) half-life

TBAC tetrabutylammonium chloride

TBAF tetrabutylammonium fluoride
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
</tr>
<tr>
<td>TBAT</td>
<td>tetrabutylammonium triphenyldifluorosilicate</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyltriphenyldifluorosilicate</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyltrimethylsilyl</td>
</tr>
<tr>
<td>temp</td>
<td>temperature</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TES</td>
<td>triethyldimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylendiamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TOF</td>
<td>turnover frequency</td>
</tr>
<tr>
<td>TON</td>
<td>turnover number</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>TROC</td>
<td>trichloroethoxycarbonyl</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl or p-toluenesulfonic</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>Vis</td>
<td>visual wavelength</td>
</tr>
<tr>
<td>v/v</td>
<td>volume per volume</td>
</tr>
<tr>
<td>wt%</td>
<td>percent by weight</td>
</tr>
<tr>
<td>w/v</td>
<td>weight per volume</td>
</tr>
<tr>
<td>X</td>
<td>halide or trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen olefin geometry</td>
</tr>
</tbody>
</table>