

Design and Development of New Enantioselective Catalytic Reactions and
Progress towards the Total Synthesis of Callipeltoside A

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

2004

(Defended 20 January 2004)

□ 2004

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This thesis is dedicated to David, Mommy, and Da with more love than I can express

Acknowledgements

The MacMillan group has, since its inception, adhered to a level of excellence that can be as powerfully exciting as depressingly backbreaking in its intensity. These standards have been set by my adviser, David MacMillan, and I must thank Dave for being a model to me of the scientific method, of the necessity to strive for perfection in research. But more, Dave holds dear the pursuit of new understandings, and this passion is infused deep within his research group. I cannot thank him enough for helping me both to harness the elements of that drive that are within myself and to use that drive to perform as I have during these five and a half years.

My interest in chemistry was first given structure by Professor David Evans, with whom it was my incredible privilege to engage in research during my final two years of college at Harvard. The skills and knowledge I gained from Dave and his powerful group of researchers gave me supreme confidence as I headed to tackle the challenges of graduate school, and his continued absolute support has been invaluable as I have made my way through school and towards the workplace.

Before I knew that synthetic organic chemistry would be my field of choice, I was fortunate enough to work with Professor Peter Politzer at the University of New Orleans. For three summers, Peter was an involved mentor, taking a real interest in my education as he saw me through the jungle of theoretical physical chemistry. Peter's support has been crucial to the growth of my chemical career. I cannot overstate the extent of the opportunities my relationship with Peter has afforded me, nor can I thank him enough for his role in my education.

I would like to thank the members of my committee at Caltech, Linda Hsieh-Wilson, Bob Grubbs, Rudy Marcus, and Dave, for all of their time and effort. I would also like to extend my thanks to the members of my candidacy committee at Berkeley, Jean Fréchet, Peter Volhardt, Doug Gin, and James Berger. Making the acquaintance of Professor Fréchet has been a particular delight, and I am grateful for his assistance and encouragement. I would also like to acknowledge Brian Stoltz, with whom I had the pleasure of teaching in my first year at Caltech, for his dedication to education and the interest he has always taken in my research.

My time in graduate school was made all the easier thanks to the expert assistance and counsel of Selina Fong during both the Berkeley and Caltech years. I would like to thank as well Lynne Martinez, Dian Buchness, and Chris Smith for making my transition to and time at Caltech a pleasure. Rudi Nunlist of Berkeley's NMR facility, Tom Dunn and the late Dr. Lee of Caltech's NMR facility, and Mona Shahgholi of Caltech's mass spectrometry facility have been very helpful to me during my research.

The members of the Heathcock, Ellman, and Bergman research groups at Berkeley were instrumental in our first two years as a research group, as generous with their chemicals as they were with their chemical advice. The Grubbs and Stoltz groups at Caltech have been constant sources of materials and discussion as well.

A very special thanks to Dr. Jeongbeob Seo for his work on the total synthesis of callipeltoside. Jeongbeob was a wonderful member of the lab — responsible, hard-working, and kind, and it was my great pleasure to be involved with callipeltoside after he left the group. Thank you to Wendy Jen for her work on the dipolar cycloaddition project.

One of my truly favorite parts of graduate school has been the chance to work with extremely talented undergraduates. My first teaching experience came at Berkeley with Big Section 521; it was wonderful to watch my students grow into organic chemists. While in the MacMillan group, I thrived in working with and helping to train Jennifer Tam, Naomi Anker, Thanh Thai, and Kevin Andruss in the ways of synthetic organic chemistry.

I have nothing but the utmost respect for and deepest thanks to all those alongside whom I have worked in the MacMillan group. Together we surmounted innumerable challenges and have built one hell of a research group — we have taken from each other as much as we have given, and this bond, for better and worse, is one that will always unite us. No one works like we work, and no research group in the history of science has put together a more dominant athletic machine than has the MacMillan Group. Whether going undefeated in softball, crushing the Stoltz group in touch football, wiping the soccer field with the carcasses of so many vanquished opponents, or laying down the law in the GSC basketball league (where thankfully they don't keep track of your fouls), we have been unstoppable.

Joel Austin has an extremely positive and rational presence in the lab, and I thank him for being Joel Austin and a great friend and arm-wrestler. Ian Mangion and Broiler have provided me with consistently high-quality entertainment. Though each is great on his own, our three-way political discussions are unsurpassed — you both helped me to refine my thinking and forced me to consider new and often ridiculous, but more often intelligent, positions. Thanks to Nikki Goodwin for being unpredictable, sweet, and generous. Stripy Katie Saliba, who never ever sleeps, and Sandra Lee always met me with huge smiles, making a big difference in my final years of school. Playing lab sports with Mike Brochu, Sean Brown, Dr. Chris Sinz, and Rob Knowles showed me what real athleticism was about. My time spent at the beach with Dr. Simon Blakey was almost as much fun as our time as neighbors in the lab. He possesses a wonderfully sarcastic wit, a profound intelligence, incredible speed, and a charming craftiness — he is a true player. Dr. Roxanne Kunz has never let me get away with anything, and I liked that. DOUG Moncure made sharing a desk, bench, and hood a real pleasure. Unceasingly positive, DOUG never failed to make me happy when I was at my grumpiest. I know that we will always be united by our love for the Los Angeles Lakers and the Democratic Party. Alan Northrup is scarily smart and works far too hard, and, moreover, he is just a really good person with a heart of gold. I spent three and a half years working next to the Train, and I am deeply grateful to him for the unending generosity with which he dispensed advice and interest. He and I kept things real, you know what I'm saying?

I want especially to thank the first group — Chris Borths, Kateri Ahrendt, Tristan Lambert, Wendy Jen, Vy Dong, and Tehshik Yoon. The experience we have shared was one of the greatest times of my life. In particular, Tehshik Yoon was a completely selfless leader in our young lab — he trained all of us from the ground up, showing us what it meant to be a student of chemistry. We drove him crazy, but not once did he hesitate to help us. Thank you to Borths whose silliness and tremendous quotability have made lab-life more fun, and whose Mr. Fix-It status in the lab is unequaled.

Vy, you have been a true friend to me during graduate school. I am not sure who had more points at the end, but I think we're both pretty good chemists. We have laughed and cried together, in the embrace of our future selves, and I know our friendship grow as we move into the next phases of our lives.

The medical profession has made a load of money off of me during my time in graduate school. Thanks to the emergency room staff at Alta-Bates Hospital in Berkeley for repairing me in the aftermath of a late-night bike accident and to Drs. Bryan Krey and Bill Cavalli for their subsequent work in putting my face back together and giving me my super titanium teeth. In Pasadena, I would like to thank the Huntington Memorial Hospital emergency room staff for the countless X-rays, the lovely stitches, and the one staple they put in my head during my time at Caltech. Drs. Steven and Charles Battaglia did a great job fixing a broken nose (for obvious reasons, my nose required both of them). I extend a very special thanks to Dr. Elizabeth Shon in Pasadena who has been a great help to me as I have learned about myself during the last few years.

Thanks to the Penultimate crew, especially Leslie Dunipace, for affording me the chance to have consistent fun-filled athletic competition and bloody knees. Thank you to my always dear college buddies Tom Flores, Charles Wong, and Robert Wolinsky. Go Cabot House!!! Akiko Tarumoto has been a fabulous roommate and friend for the last year and a half, and I wish I had met her sooner.

I will miss Chad Schmutzer more than anything when I move to San Diego – Chad, I am always laughing with you and laughing harder than I ever thought possible, and I feel Lucky to have you in my life.

I am incredibly fortunate to have met Dr. Ioana Drutu, and I can't wait to see what wonders unfold as we create our life together.

Justice and all of the members of Team Justice will always be close to my heart (and bicep). The core: Dan Sanders (of “Dan Sanders Special” fame), Matt Pohlman, Brian Johnson, and Chad. Also, Brian “B-agel” Leigh, Jim Falsey, Ted Betley, Steve Brown, Anand Vadehra. JUSTICE. You guys made life in grad school awesome and every Saturday full of not only big fun and laughs, but also truly exceptional football. Fasten your seatbelts...Team Justice is coming to get you!

My family has supported me always. I have realized in the last year that when I think about what it means to be a responsible member of society, to be an intelligent and good person, I am simply thinking about my parents. And no one could have a better friend than I do in my brother David. Sweet, funny, smart, strong, humane. My bro.

Abstract

The development of a new enantioselective catalytic *anti* aldol reaction is described. In this Lewis acid-catalyzed process, a chiral metal-ligand enolate complex is accessed through soft-enolization and reacts with an aldehyde to form aldol adducts in good enantioselectivity and *anti* diastereoselection. Mechanistic studies confirm the non-Mukaiyama pathway involving a reactive metal enolate species. Investigations have shown that the choice of amine base has a remarkable effect on the mechanism and outcome of the reaction.

The development of the first enantioselective organocatalytic [1,3]-dipolar cycloaddition reaction is also reported. In this imidazolidinone-catalyzed process, nitrones react with α,β -unsaturated aldehydes to form chiral isoxazolidines in excellent yield, enantioselectivity, and diastereoselection. The scope of this process appears quite general with respect to both the nitrone and aldehyde components of the reaction. A second-generation imidazolidinone catalyst offers improved reaction rates and selectivities and has also facilitated the development of the first *exo* selective organocatalytic [1,3]-dipolar and Diels-Alder cycloaddition reactions.

A synthetic approach towards the marine natural product callipeltoside A is described. The synthesis relies upon rapid construction of the stereochemical backbone through a novel tandem amino-sulfide acyl-Claisen rearrangement. Subsequent elaboration towards the macrolide has involved a highly diastereoselective reductive opening of a spirocyclic intermediate, highly diastereoselective Ireland Claisen rearrangement, and synthesis of the tetrahydropyran moiety through a palladium catalyzed carbonylative cyclization. Completion of the synthesis has yet to be achieved due to difficulties in removal of a benzyl ether protecting group.

Table of Contents

Acknowledgements	iv
Abstract	viii
Table of Contents	ix
List of Schemes	xii
List of Figures	xiv
List of Tables	xv

Chapter 1. Merging Enolization and Enantioselective Catalysis: Development of a Direct Enantioselective Catalytic *anti* Aldol Reaction

I. Introduction	1
II. Results and Discussion	7
Acetate ester aldol reaction	7
Evidence supporting a metal enolate intermediate	9
Propionate ester aldol reaction	11
β -Benzyloxy ester aldol reactions	14
Evidence supporting a metal enolate intermediate and stereochemical rationale	15
Degradation of selectivity	17
Mechanistic investigations	21
Limitations and future directions	25
III. Conclusion	26
IV. Experimental Section	26
V. References	35

Chapter 2. Development of the First Enantioselective Organocatalytic Dipolar Cycloaddition Reaction and Enantioselective Organocatalytic *Exo*-selective Cycloadditions

I. Introduction	39
-----------------	----

Organocatalysis	39
LUMO-lowering activation	42
1,3-dipolar cycloadditions between nitrones and olefins	43
Initial optimization of the enantioselective organocatalytic dipolar cycloaddition	47
II. Results and Discussion	49
Catalyst design and reaction optimization	49
Substrate scope	56
Stereochemical rationale	58
Limitations	59
Second-generation imidazolidinone catalyst design and implementation	60
III. Conclusion	65
IV. Experimental Section	66
V. References	96
Chapter 3. Progress towards the Total Synthesis of Callipeltoside A	99
I. Introduction	99
Isolation and biological activity	99
Synthetic approaches to callipeltoside A	100
Tandem amino-sulfide acyl-Claisen rearrangement	106
II. Results and Discussion	109
Retrosynthetic analysis of callipeltoside A	109
Synthesis of precursor to the tandem amino-sulfide acyl-Claisen rearrangement	111
Tandem amino-sulfide acyl-Claisen rearrangement	112
<i>Anti</i> reduction of α -hydroxy ketone and Ireland Claisen rearrangement	114
Acetylide opening of epoxide	120
Ireland Claisen rearrangement	122
Tetrahydropyran formation	125

III. Conclusion	127
IV. Experimental Section	128
V. References	163

Chapter 4. Summary of Doctoral Research

I. Design of a Conceptually Novel Lewis Acid-Catalyzed Enantioselective <i>Anti</i> Aldol Reaction	166
II. Enantioselective Organocatalytic [1,3]-Dipolar Cycloaddition and <i>Exo</i> Selective Cycloaddition Reactions	167
III. Progress Towards the Total Synthesis of Callipeltoside A	170
IV. References	173

Appendix 1. X-Ray Crystallographic Data for (3*R*,4*S*)-2-Benzyl-

4-formyl-3-naphthylisoxazolidine	174
----------------------------------	-----

List of Schemes

Chapter 1

Scheme 1. Proposed catalytic cycle	6
Scheme 2. Enolate geometry and diastereoccontrol in the aldol reaction	14
Scheme 3. Degradation of selectivity.....	18
Scheme 4. Proposed rationale for observed degradation of selectivity	19
Scheme 5. Silylated aminol intermediate leads to open transition state	23
Scheme 6. Free aldehyde leads to closed transition state.....	24

Chapter 2

Scheme 1. Proposed catalytic cycle for organocatalytic dipolar cycloaddition	46
Scheme 2. Calculated (MM3) iminium isomer predicts stereochemistry of cycloaddition	59
Scheme 3. Second-generation catalyst should afford higher reaction rates	61
Scheme 4. Second-generation catalyst should afford increased enantioselectivity.....	62

Chapter 3

Scheme 1. Trost's retrosynthesis of callipeltoside A	101
Scheme 2. Evans' retrosynthesis of callipeltoside A	103
Scheme 3. Paterson's retrosynthesis of callipeltoside A.....	105
Scheme 4. Proposed tandem amino-sulfide acyl-Claisen rearrangement	108
Scheme 5. Stereochemical rationale for the tandem amino-sulfide acyl-Claisen rearrangement.....	109
Scheme 6. First-generation retrosynthesis of callipeltoside A	110
Scheme 7. Enantioselective synthesis of acyl-Claisen precursor	111
Scheme 8	112
Scheme 9. Installation of \square -oxy ester	115
Scheme 10. Jackson's <i>anti</i> reduction of cyclic ketones	116

Scheme 11. Bu_4NBH_4 reduction stereochemistry as a function of solvent.....	117
Scheme 12. Ireland Claisen rearrangement.....	118
Scheme 13. Spirocyclization leads to revised retrosynthesis	119
Scheme 14. Reductive opening of spirocycle.....	120
Scheme 15. Marshall carbonylative cyclization	121
Scheme 16. Formation of terminal epoxide.....	122
Scheme 17. Synthesis of Ireland Claisen precursor.....	123
Scheme 18. Synthesis of carbonylative cyclization precursor.....	125

Chapter 4

Scheme 1. Proposed catalytic cycle for novel aldol reaction	166
Scheme 2. Tandem Claisen provides access to callipeltoside A	170
Scheme 3. Preparation of enantiopure allylic amino-sulfide.....	171
Scheme 4. Tandem amino-sulfide acyl-Claisen rearrangement	171
Scheme 5. Synthetic route subsequent to tandem acyl-Claisen rearrangement.....	172

List of Figures**Chapter 1**

Figure 1. Representative chiral ligands examined in the aldol reaction.....	9
Figure 2. Calculated substrate-catalyst complex	17
Figure 3. Effect of amine base on the aldol reaction.....	21
Figure 4. ReactIR investigation reveals aldehyde consumption.....	22
Figure 5. Detection of silylated aminol by ^1H NMR	23

Chapter 2

Figure 1. Lewis acid binding to nitrones	45
Figure 2. Iminium ion geometry control affects enantioselectivity	48

Chapter 3

Figure 1. Callipeltoside A.....	99
Figure 2. Ruthenium-catalyzed Alder-ene reaction	101
Figure 3. Trost's synthesis of the callipeltoside core.....	102
Figure 4. Evans' synthesis of the callipeltoside macrolactone.....	104
Figure 5. Paterson's synthesis of the callipeltoside macrolactone.....	106
Figure 6. Acyl-Claisen rearrangement	107
Figure 7. Sulfide acyl-Claisen rearrangement	107

Chapter 4

Figure 1. Direct <i>Anti</i> Aldol Reaction	167
---	-----

List of Tables**Chapter 1**

Table 1. Preliminary results.....	8
-----------------------------------	---

Chapter 2

Table 1. Effect of catalyst structure on the dipolar cycloaddition between crotonaldehyde and nitrone 3.....	50
--	----

Table 2. Effect of solvent on the dipolar cycloaddition reaction between crotonaldehyde and nitrone 3.....	52
--	----

Table 3. Effect of amount of water on the dipolar cycloaddition of crotonaldehyde with nitrone 3	53
--	----

Table 4. Effect of reagent molarity on the dipolar cycloaddition of crotonaldehyde with nitrone 3	54
---	----

Table 5. Effect of the Brønsted acid co-catalyst on the dipolar cycloaddition between crotonaldehyde and nitrone 3	55
--	----

Table 6. Organocatalyzed dipolar cycloadditions between representative nitrones and crotonaldehyde	57
--	----

Table 7. Organocatalyzed dipolar cycloadditions between representative nitrones and acrolein	58
--	----

Chapter 4

Table 1. Organocatalyzed dipolar cycloadditions between representative nitrones and dipolarophiles.....	169
---	-----