PROGRESS TOWARD AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF INELEGANOLIDE

Thesis by

Jennifer Lyn Roizen

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To James Mrazek,

Who remains a daily reminder of what a privilege it is to be at Caltech.

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When I decided to work for Brian, I wanted to work for someone who did chemistry that wasn't just interesting, but was interesting enough to make me jealous of the students who developed it. That's the best gift Brian could have given me, and he has. Brian identified ineleganolide as a target to test the key Wolff/Cope rearrangement. He welcomed me onto this project, and into his group. He brought creative insights and an infectious enthusiasm to discussions. His conceptual suggestions helped to mold this research, enabling or inspiring us to skirt daunting chemical challenges. He secured funding. Finally, he forced me to understand that I am the guardian of this project's two legacies — its chemical advances, and my education.

My committee consisted of several of the "most interesting chemists in the world" — an accomplished group of mentors who always treated me with respect. I am a better chemist for their attention. John Bercaw has been supportive committee chair from the start, patiently wading through and critiquing my ideas. Dave MacMillian let me into Caltech. He took time to astound me with his results, and to force me to state my rationale for selectivity and reactivity (in committee and class). Bob Grubbs and Dennis Dougherty have developed a friendly atmosphere throughout my time at Caltech, and kindly joined my committee in my fifth year. Bob has a completely different (and excellent!) approach to synthetic methodology development (than Brian), which I've learned from primarily by sitting in on a few of his group meetings. Dennis is a precise and articulate chemist, and I'm convinced that he could master any field of chemical knowledge. Sometimes it seems he already has (conquered every field).

Sarah Reisman joined the organic division in my final year at Caltech. On her arrival, 8 of us invaded her space in the Church basement. We had a birds-eye-view of her group as they built her research program. Sarah has proven an excellent role model and friend — a level-headed, patient, and considerate chemist.

Scott Virgil brought his deep chemical knowledge and attention to detail to Caltech during my fifth year (2007). His insights were instrumental in assigning unanticipated structures based on simple proton Nuclear Magnetic Resonance (NMR) spectra, and understanding failed transformations. He also developed LC/MS assays and methods to use reverse-phase HPLC to purify late stage compounds.

…

I have been fortunate to join several collaborators on this journey: Richmond Sarpong, Julius Su, Masaki Seto, Amanda Jones, Amanda Silberstein and Dave Romney.

I would have been lucky just to join a lab with Richmond in it. He leads by example with impressive charisma and dedication. Richmond showed me around the lab during visiting weekend, and was unfazed by a fusillade of questions. On my arrival, I joined him on the Wolff/Cope project, and briefly invaded his bench. He has been an excellent mentor and constant support, even at a distance.

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Masaki Seto visited from Takeda Pharmaceutical Company Limited of Japan from February 2007–2008. Together, we built on the framework established by Doug Behenna, JT Mohr, Nat Sheridan, Dave White, and many others to develop the

enantioselective alkylation of substituted dioxanone enol ethers to access tetrasubstituted hydroxycarbonyl compounds. Masaki was the first to explore silyl enol ethers in this context, and humored many of my suggestions for optimization. Without Masaki, scale-up for ineleganolide would have remained impossible.

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In my time here, I've worked next to 16% of the postdoctoral scholars or grad students who have come through this lab, including Ryan McFadden, Gene Lee, Dan Caspi, Dave White, Andy Harned, Zoltan Novak, Xiaoquin Han, Corinne Baumgartner, Matt Winston, Kevin Allen, John Enquist, Kim Petersen, and Tomoko Ashizawa. Each of them has heard me whistle, seen me dance and sing, and put up with less pleasant moments. And each of them has taught me a lot.

Ryan McFadden is a genuine, caring, and thoughtful human being who has demonstrated unwavering commitment to chemical research. Gene Lee joined me and Ryan for a few months, and shared his life with our bay.

I had new desk / baymates in the Gates Annex. I became a much better chemist while working next to Dan Caspi and David White. Dan Caspi was a meticulous macro-making machine. He streamlined the thesis-writing process. He's an expert at critiquing synthetic presentations and taught me to demand a clear story that's depicted in crisp

horizontal storyboards. Dave White brought from Harvard crafty column-loading techniques and a keen interest in mechanism. He focused this interest on the palladium-catalyzed decarboxylative allylation and used it to provide a handful of fruitful suggestions. Dan and Dave witnessed (and catalyzed) the most dramatic improvements in my abilities as an experimentalist. Professor Andy Harned brought a talkative and chatty approach to chemistry, and a deep knowledge of cost-saving measures. Professor Zoltan Novak was kind enough to let me have the bench with a window, and adventurous enough to embrace challenging projects. As they moved on, Xiaoquin Han and Corinne Baumgartner brightened my life with their spotless benches, new natural products, and comfortable kindness.

The final addition to the Gates first floor was Matt Winston, who became my baymate in the move to the Church basement. Matt Winston was an extremely generous and genuine individual. I felt like he spent the past year offering me cookies and cream puffs. He expected to have fun every moment of every day in lab, and that really raised the bar for the bay. He relished the opportunity to think deeply about chemical transformations.

Within constant earshot, Kevin Allan and John Enquist are a comic duo, who banter about chemistry with ease, discipline, and curiosity. It is a game to them. Kim Petersen has been a great friend, pairing chemical creativity with personal intuition, and a great taste in entertainment. More recently we have been joined in the basement by Tomoko Ashizawa and Josh Day, who brighten our lives with consistent kindness.

I have learned as much from my entering class as from my baymates. JT has a formidable knowledge of physical and analytical chemistry. He uses language precisely,

and has a fruitful impatience with chemistry. Krout demonstrates exemplary perseverance and thoroughness, and has provided unwavering encouragement. Finally, Meyer (along with John Phillips) waded his way through a project (BSK) with similar design and challenges.

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Most of the Stoltz group loves to talk about chemistry, but everyone has their own style. In addition to my deskmates and projectmates and classmates, I enjoyed frequent (perhaps daily) chats with Chris Henry, Dave Ebner, Hosea Nelson, Nat Sherden, and Jan Streuff! They were always willing to talk shop. Chris Henry arrived around the same time as a new mass spec, and brought with him the knowledge of how to use it, as well as an abiding interest in NMR puzzles and southern courtesy. Despite his youth, he has been a generous (with time) editor, a driven chemist, and a kind friend. Likewise, Dave Ebner has been an insightful editor and cherished friend, as well as my source for palladium-specific knowledge. Hosea Nelson has mastered the art of submarine chemistry. He participates honestly, conscientiously, and with playful teasing. Nat Sherden has knowledge and chemical instincts that are orthogonal to mine, and the space between has been stimulating.

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Coming into this lab, I did not understand how integral intellectual risks were to research. Everyone takes them, but people limit their risks in different ways. Ryan McFadden and Allen Hong demonstrated extreme persistence in the face of failing projects. Raissa Trend and Shyam Krishnan did not limit themselves to a method, a field, or an area of knowledge. This capacity lent Raissa and Shyam to awe-inspiring breadth. Incidentally, Raissa was an excellent communicator, and Shyam voiced a shower of knowledge-laden questions (as did JT and Andy McClory).

A friend told me that when you leave a place, you must get to know your younger peers, so you can maintain a connection with that place. The energetic rookies of the Stoltz (Jonny Gordon, Alex Goldberg, Nathan Bennett, and Boram Hong) and Reisman (Jay Codelli, Raul Navarro, Erin Lamb, Lindsay Repka, Roger Nani, and John Yeoman) labs have been a breath of fresh air. If they can do for chemistry what they do for group morale, we will easily achieve Brian's goal of being the best groups in the world. No pressure.

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…

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…

If you've spoken to me, even once, since 2003, there's a good chance that you know I love Williams College. There, Professors Thomas E. Smith and the late J. Hodge Markgraf let an excited, but inexperienced undergraduate play with highly reactive chemicals *en route* to Hennoxazole A (TES) and benzoisocanthinones (JHM). They nurtured my inclinations toward synthesis with patience and generosity. These great teachers and chemists have earned my respect and affection.

…

This experience has paved the way to another: I am excited to join the Du Bois group at Stanford. Justin Du Bois shared unpublished results with me, which helped me to develop one of the research proposals. Wan-Chao Chang facilitated submission of my fellowship applications, with unparalleled patience, organizational skills, and impressive initiative. Finally, Rose Conrad bridged the gap between me and the Du Bois group. She provided me with advice, copies of theses, chemical insights, and friendship. She is an insightful chemist, who has delved deeply into interesting chemical challenges to produce a body of work of high quality. It has been a privilege to get to know her.

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ABSTRACT

Investigations toward an enantioselective total synthesis of ineleganolide (**1**) are disclosed. These studies have driven the development of a novel asymmetric ketone alkylation to form C(α)-tetrasubstituted carbonyl compounds. Products of these alkylations have been converted to α-hydroxy ketones, acids, and esters, completing an asymmetric formal synthesis of (–)-quinic acid.

Additionally, one of these products, a chloroalkene, has been advanced in the synthesis of the [6–7–5–5]-fused core of ineleganolide. The chloroalkene can be converted through a mild oxidative bromination, Wittig olefination, and Luche reduction sequence to rapidly access the enantioenriched cyclopentenol fragment of ineleganolide. Two of these alcohols can be coupled with a cyclohexenone-derived carboxylic acid to append the six-membered ring fragment. These flexible vinylogous β-ketoesters can be advanced to a rigid [5–5–3]-fused cyclopropane.

At the outset of this work, we envisioned the advancement of a [5–5]-fused cyclopropane through a tandem Wolff/Cope rearrangement to access the [6–7–5–5]-fused core of ineleganolide. Synthetic studies toward this rearrangement are described. Additionally, we explore a translactonization/Cope rearrangement and a cyclopropanation/Cope/epoxidation cascade sequence to access the [6–7–5–5]-fused scaffold. In the course of these efforts, a rich body of chemistry has been developed exploring translactonizations in *cis*-substituted cyclopentane diols, including the translactonization/Cope cascade.

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl, acetate
acac	acetoacetate
app.	apparent
aq	aqueous
atm	atmosphere
BBKIE	bond breaking kinetic isotope effects
BMKIE	bond making kinetic isotope effects
Bn	benzyl
bp	boiling point
br	broad
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
Bz	benzoyl
c	concentration for specific rotation measurements
°C	degrees Celsius
calc'd	calculated
cat.	catalytic
CCDC	Cambridge Crystallographic Data Centre
$Cu(tbs)_2$	bis(*N*-*tert*-butylsalicylaldehydiminato) copper (II)
d	doublet
dba	dibenzylideneacetone

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMAPP	dimethyl allyl diphosphate
dmdba	3,5,3',5'-dimethoxydibenzylideneacetone
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EC_{50}	median effective concentration (50%)
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
FPP	farnesyl diphosphate
fs	femtosecond
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
gHMBC	gradient-heteronuclear multiple bond correlation
GGPP	geranylgeranyl diphosphate
h	hour(s)
HPLC	high performance liquid chromatography

HRMS	high resolution mass spectroscopy
$h\nu$	light
Hz	hertz
IC_{50}	median inhibition concentration (50%)
IPP	isopentyl diphosphate
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
L	liter
LDA	lithium diisopropyl amine
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet or milli
m	meta
m/*z*	mass to charge ratio
μ	micro
M	molar
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MTM	methylthiomethyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
[O]	oxidation
o	ortho
p	para
*p*ABSA	*p*-acetamidobenzenesulfonyl azide
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
PHOX	phosphinooxazoline
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
Py	pyridine
q	quartet
ref.	reference
R	carbon-containing substituent
R_f	retention factor
$Rh_2(oct)_4$	rhodium octanoate
rt	room temperature
s	singlet or strong or selectivity factor

SAMP	(+)-(*S*)-1-amino-2-methoxymethylpyrrolidine hydrazones
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
(*S*)-*t*-Bu-PHOX	(4-(1,1-dimethylethyl)-2-[2-[diphenylphosphino)phenyl]-4,5-dihydro-(4*S*)-oxazole)
TBHP	*tert*-butyl hydroperoxide
tbs	*N*-*tert*-butylsalicylaldehydiminato
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
w	weak
w/*v*	weight to volume
v/*v*	volume to volume
X	anionic ligand or halide