

To Marcia

for her love and support

Acknowledgments

There are so many people I want thank for guiding me during my graduate student years. First and foremost, I am grateful to my advisor and mentor, Brian Stoltz. He has encouraged and challenged me from the very first day I arrived in the lab. His passion for chemistry is contagious, and he is a creative teacher who makes our science come to life. I truly admire the tenacity, openness, and flexibility he models to us, his students, as he manages our laboratory. He has given me incredible academic opportunities, allowing me to tackle both methodology and total synthesis while granting me freedom to explore my own ideas. The advice and support he has lent me over the years will never be forgotten.

I am also grateful to my committee members. My chairperson, Professor Bob Grubbs, encouraged me when my science was challenging, helping me to find my niche as a chemist. I have enjoyed my interactions with Professor Goddard and his group over the years. Our collaborations on both hypervalent iodine and palladium chemistry have been rewarding. Professor Hsieh-Wilson has also played a key role during my time at Caltech, helping give me a deeper understanding about biochemistry, inspiring me as I begin a career in medicinal chemistry. Although not an official committee member, I also want to thank Professor Dervan. It was a joy helping teach his class, and our discussions about science were rewarding.

I want to express my gratitude to Dr. Hicham Fenniri for mentoring me while I was an undergraduate in his lab at Purdue University. His encouragement for me to pursue graduate work in organic chemistry was valuable, and he taught me the importance of effective scientific communication. His patience and fascination with chemistry were great models to me. Professor Timothy Zwier is also acknowledged, as

are the many students in his lab at Purdue who took the time to mentor me during my first undergraduate research experience.

A special thanks also goes to Eli Lilly for their funding of my research and education over the years, especially in graduate school. Neil Rapp, Mike Kelly, Jim Schwengel, Kelly Kuchenbrod, and Jim Kimsey also deserve a warm thanks. These teachers helped foster my love of learning and went out of their way to give me opportunities to grow as a scientist. It all started with that vinegar and baking soda science fair project!

It has been a privilege to collaborate with so many talented scientists over the years. Dan Caspi and Dave Ebner were my first partners in crime. In our early days we investigated many flavors of oxidative kinetic resolutions. We used to draw straws to see who would get the GC next? One of us always got stuck doing runs at 4 a.m.—it built character, though! It was also a joy to work with Julius Su from the Goddard group on hypervalent iodine chemistry. He is an enthusiastic, friendly, and brilliant person, and I wish him continued success. Thanks goes to Scott Virgil for helpful discussions—he is always excited to talk chemistry, and we are glad to have him at Caltech.

Next, I want to give a shout out to my baymates past and present. John “JZ” Zepernick was a hard-working guy with an ability to make anybody laugh about anything. It was always lively when we chatted about politics, and it wasn’t surprising when he went to campaign for Howard Dean because he was doing what he loved. Jenny Roizen was a very personable baymate, and continues to be a great friend. Our conversations about everything from Dave Matthews to Dar Williams were memorable. Gene Lee showed that you could do chemistry and still be a family man. Nat Sherden and

I had so much fun talking about chemistry that it's a wonder we actually got any done! He introduced me to Zwan, the Smashing Pumpkins, and other great music. We had this barbecue once—I've never seen someone eat so much steak! Last, but not least, is Narae Park. Her bubbly enthusiasm is awesome, and I have learned a lot about chemistry from her. She has really encouraged me and helped me laugh at my mistakes! And what would graduate school have been like without Jenn Stockdill, my unofficial baymate? Whenever chemistry was going rough she'd be around to cheer me up and get me thinking about solutions instead of problems. Not only is she a talented chemist, but also a true friend. She was always game for ice cream, coffee, or Amigo's—whichever was in order!

I want to thank all of the postdocs who have come through the Stoltz Lab too. Richmond Sarpong was a mentor and taught me the ropes when I was a newbie in the lab. Zoltán Novák was my lunchtime friend, and we'd compare/swap dishes our wives had made. He showed me what REAL Hungarian goulash was supposed to taste like. Charles Liu is a talented chemist and made short work of some tough natural products. I look forward to seeing him again when I get to Gilead; they are privileged to have him on their team. A huge thanks goes out to Dave White for his advice, wisdom, and suggestions about the job interviewing process. It was a great experience working with him and Mike Krout on the enantioselective decarboxylative alkylation chemistry.

I owe Neil Garg a big thanks for taking the time to help me get started in the lab. When I came to Caltech as a prospective student, I remember meeting him and seeing how much he loved working for Brian. Whether he was taking prospectives for a hike to Switzer's or presenting a poster, Neil went out of his way to make us feel welcome. His enthusiasm really got me excited to join the Stoltz lab, and I am so glad that I did.

A special thanks goes out to Team Tsuji, including Doug Behenna, JT Mohr, Andy Harned, Kousuke Tani, Sandy Ma, Nat Sherden, Jeff Servesko, Akihiko Iwashita, Smaranda Miranescu, John Keith, Julius Su, Jenny Roizen, John Enquist, Mike Krout, Dave White, Toyoki Nishimata, Masaki Seto, Thomas Jensen, and anyone else I may have forgotten. The length of this list is a huge tribute to Doug Behenna, who performed some of the first investigations into the enantioselective Tsuji allylation. His insight and discoveries have paved the way for numerous projects in the group, including my own.

I also want to thank Dr. Gomez and Dr. Selke from Cal State LA, as well as the PREM program. It was an honor to speak at the 2006 inaugural PREM conference in San Diego, and it was a fantastic experience working with Jacqueline Malette. Although she may have learned things from me while I was her mentor for two summers, I think I learned even more. A huge thanks also goes out to the Caltech MURF program, which made the experience possible.

There are many behind-the-scenes folks who are the oil for the research engine. Scott Ross and Chris Brandow have kept our NMR facility running and have gone out of their way on several occasions to help me out. Mona Shahgholi and Naseem Torian have been a huge help with mass spectrometry needs. If it is broken, Tom Dunn can fix it. I can't even keep track of all of my broken stirplates he's repaired. Rick Gerhart has repaired an equally large number of my broken flash columns. Mike Day and Larry Henling have helped provide the X-ray crystallographic data presented in this thesis. Dian Buchness and Laura Howe have helped immensely with the administrative details of my time here—more than I'm probably aware of!

My parents have shown me so much love and support, and worked so hard to provide me with opportunities that helped bring me here. The Liems are my new family and have provided me great comfort, love, and hospitality. Erin, Kevin, Pete, and Kimi, thanks for cheering me on, saying, “You can do it!” God has helped me through. Finally, I want to thank my loving wife, Marcia. Her care, support, prayers, and encouragement have kept me going. And I know the lab will miss her awesome cooking!

ABSTRACT

The catalytic enantioselective preparation of all-carbon quaternary stereocenters within rings via alkylation is a major challenge in synthetic organic chemistry. Many important natural products and biologically active pharmaceuticals contain this motif. We have developed palladium-catalyzed decarboxylative alkylations capable of generating all-carbon quaternary stereocenters in good yield with high enantioselectivity.

Alkylated products are readily elaborated to synthetically useful cyclic scaffolds. The enantioselective decarboxylative alkylation is thus utilized to prepare intermediates previously reported in the total syntheses of classic natural products. Herein, we disclose modern formal syntheses of (−)-Thujopsene, (−)-Dysidiolide, and (−)-Aspidospermine.

The longer-term goal was to apply this new enantioselective catalysis to the total syntheses of natural products with novel carbocyclic architectures. Our methodology is demonstrated during the first protecting group-free enantioselective total synthesis of (+)-dichroanone, a 4a-methyltetrahydrofluorene. The [6-5-6] tricyclic natural products family has members with important biological activity, and our route to (+)-dichroanone may provide general access to related compounds. During our synthetic endeavors, a novel Kumada-benzannulation approach to the aromatic portion of (+)-dichroanone was developed, along with a unique synthesis of a hydroxy-*p*-benzoquinone from a phenol. The absolute stereochemistry of the natural product was verified for the first time during our total synthesis.

Significant progress has been made toward the total synthesis of the marine meroterpenoid liphagal, a potent and selective phosphatidylinositol 3-kinase α inhibitor. The enantioselective decarboxylative alkylation has been employed, and an acetylene [2 + 2] photoaddition / ring-opening sequence is used to construct the 7-membered ring. New understanding about the reactivity of [6-7] bicyclic scaffolds has been gathered, and the information applied during preparation of liphagal's benzofuran motif. Our efforts have led to a functionally diverse array of liphagal analogues, which may be used for structure-activity-relationship studies with phosphatidylinositol 3-kinases.

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List of Abbreviations

2,6-DTBP	2,6-di- <i>tert</i> -butyl pyridine
2D-TLC	2-dimentional thin-layer chromatography
$[\alpha]_{D}^{xx}$	specific rotation at xx °C at the sodium D line wavelength
Å	angstrom
Ac	acetyl
Am	amyl
app.	apparent
aq	aqueous
Ar	aryl substiuent
atm	atmosphere(s)
BINOL	1,1'-bi-(2-naphthol)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
Bu	butyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	<i>normal</i> -butyl
<i>s</i> -Bu	<i>secondary</i> -butyl
<i>t</i> -Bu	<i>tertiary</i> -butyl
<i>tert</i> -Bu	<i>tertiary</i> -butyl
¹³ C	carbon 13 isotope
c	centi

<i>c</i>	<i>cyclo</i> or concentration (value in g/dL, for optical rotation)
calc'd	calculated
CAN	ceric ammonium nitrate
CCDC	Cambridge Crystallographic Data Centre
conc.	concentrated
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
δ	chemical shift of (value in parts per million)
d	doublet or day(s)
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCC	dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	di- <i>iso</i> -butyl alane
dmdba	di-(3',5'-dimethoxybenzylidene)-acetone
DMA	<i>N,N</i> '-dimethyl acetamide
DMAP	4-(<i>N,N</i> '-dimethylamino)-pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> '-dimethyl formamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
Dod	dodecyl

dppp	1,3-diphenylphosphinopropane
dr	diastereomeric ratio
ϵ	extinction coefficient
equiv	equivalents
<i>E</i>	engegen olefin geometry
ee	enantiomeric excess
EI	electron impact (method)
ESI	electrospray ionization (method)
Et	ethyl
¹⁹ F	fluorine 19 isotope
FAB	fast atom bombardment (method)
g	gram
GC	gas chromatography
gCOSY	gradient correlation spectroscopy
Grubbs II	the Grubbs second-generation metathesis catalyst
η^n	hapto, n = number of atoms coordinated to the metal
h	hour(s)
[H]	conceptual reduction
¹ H	hydrogen 1 isotope
<i>c</i> -hexane	cyclohexane
<i>n</i> -Hex	<i>normal</i> -hexyl
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry

Hz	hertz (s ⁻¹)
<i>i</i>	<i>iso</i>
IBX	1-hydroxy-1-oxo-1(λ^5),2-benz[d]-iodoxol-3-one
IC ₅₀	concentration required for 50% growth inhibition
IR	infrared (spectroscopy)
<i>J</i>	coupling constant (in Hz)
<i>J_x</i>	coupling constant with x-type of splitting
KHMDS	potassium bis(trimethylsilyl)-amide
λ_{max}	wavelength at a local maximum of absorption
LA	Lewis acid
LAH	lithium tetrahydridoaluminate
LCMS	tandem liquid chromatography / mass spectrometry
LDA	lithium diisopropyl amide
LiHMDS	lithium bis(trimethylsilyl)-amide
LRMS	low-resolution mass spectrometry
LSB	lanthanum sodium binol catalyst
μ	micro
m	multiplet, milli, or meter
<i>m</i>	<i>meta</i>
M	mega, metal, or molar (mol / L)
Me	methyl
min	minute(s)
mol	mole(s)

mp	melting point
Ms	methanesulfonyl
MS	molecular seives
MVK	methyl vinyl ketone
n	nano
<i>n</i>	<i>normal</i>
NBS	<i>N</i> -bromosuccinimide
NaHMDS	sodium bis(trimethylsilyl)-amide
NMR	nuclear magnetic resonance (spectroscopy)
nOe	nuclear Overhauser effect
nOesy-1D	1-dimensional nuclear Overhauser effect difference spectroscopy
[O]	conceptual oxidation
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
PCC	pyridinium chlorochromate
Pd / C	Pd ⁰ supported on activated carbon
PMHS	poly(methyl hydrosiloxane), trimethylsilyl terminated
PFPSH	pentafluorothiophenol
Ph	phenyl
PHOX	2-(triphenylphosphin-2'-yl)-oxazoline-derived ligand
PI3K	phosphatidylinositol-3-kinase
PI3K α	α isoform of phosphatidylinositol-3-kinase
ppm	parts per million

PPTS	pyridinium <i>para</i> -toluene sulfonate
Pr	propyl
<i>i</i> -Pr	<i>iso</i> -propyl
Pyr	pyridine
q	quartet
R	substituent group
R_f	retention factor
<i>R</i>	rectus chiral configuration
RAMP	(<i>R</i>)-1-amino-2-(methoxymethyl)pyrrolidine
REDAL	sodium bis(2-methoxyethoxy)-dihydridoaluminate
ref.	Reference
rel.	relative
s	singlet
<i>S</i>	sinister chiral configuration
<i>s</i>	<i>secondary</i>
SAMP	(<i>S</i>)-1-amino-2-(methoxymethyl)pyrrolidine
salen	<i>N,N'</i> -bis(salicylidene)-1,2-diaminoethane-derived ligand
sat.	saturated
sp	sublimation point
TBAT	tetra- <i>n</i> -butylammoniumdifluorotriphenylsilicate
TBDPS	<i>tert</i> -butyl diphenyl silyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

TLC	thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethyl 1,2-diaminoethane
TMS	trimethylsilyl
TES	triethylsilyl
TBS	<i>tert</i> -butyl dimethylsilyl
TMG	tetramethyl guanidine
Ts	<i>para</i> -toluenesulfonyl
t	triplet
<i>t</i>	<i>tertiary</i>
<i>tert</i>	<i>tertiary</i>
UV	ultraviolet
Vis	visible
w/w	weight per weight
yr	year(s)
Z	zusammen olefin geometry
