To Marcia

for her love and support

Acknowledgments

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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!

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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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2,6-DTBP	2,6-di-*tert*-butyl pyridine
2D-TLC	2-dimentional thin-layer chromatography
$[\alpha]^{xx}_{D}$	specific rotation at xx °C at the sodium D line wavelength
Å	angstrohm
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′-binapthyl
Bn	benzyl
bp	boiling point
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	*normal*-butyl
s-Bu	*secondary*-butyl
t-Bu	*tertiary*-butyl
tert-Bu	*tertiary*-butyl
^{13}C	carbon 13 isotope
c	centi

c	*cyclo* or concentration (value in g/dL, for optical rotation)
calc'd	calculated
CAN	ceric ammonium nitrate
CCDC	Cambridge Crystallographic Data Centre
conc.	concentrated
m-CPBA	*meta*-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-*iso*-butyl alane
dmdba	di-(3′,5′-dimethoxybenzylidene)-acetone
DMA	*N,N′*-dimethyl acetamide
DMAP	4-(*N,N′*-dimethylamino)-pyridine
DME	1,2-dimethoxyethane
DMF	*N,N′*-dimethyl formamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
Dod	dodecyl

dppp	1,3-diphenylphosphinopropane
dr	diastereomeric ratio
ε	extinction coefficient
equiv	equivalents
E	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
c-hexane	cyclohexane
n-Hex	*normal*-hexyl
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry

Hz	hertz (s^{-1})
i	*iso*
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)
J	coupling constant (in Hz)
J_x	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
m	*meta*
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
n	*normal*
NBS	*N*-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
o	*ortho*
p	*para*
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
PI3Kα	α isoform of phosphatidylinositol-3-kinase
ppm	parts per million

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

TLC	thin-layer chromatography
TMEDA	*N,N,N′,N′*-tetramethyl 1,2-diaminoethane
TMS	trimethylsilyl
TES	triethylsilyl
TBS	*tert*-butyl dimethylsilyl
TMG	tetramethyl guanidine
Ts	*para*-toluenesulfonyl
t	triplet
t	*tertiary*
tert	*tertiary*
UV	ultraviolet
Vis	visible
w/w	weight per weight
yr	year(s)
Z	zusammen olefin geometry