CONCISE TOTAL SYNTHESES OF Δ^{12}-PROSTAGLANDIN J NATURAL PRODUCTS USING STEREORETENTIVE METATHESIS

Thesis by

Jiaming Li

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Jiaming Li

ORCID: 0000-0001-6646-5693

To mom and dad.

ACKNOWLEDGEMENTS

I can still remember the rainy day when I walked on San Pasqual Walk five years ago during my first visit to Caltech. At that time, I never expected I would meet so many wonderful people with their help and support at this campus.

It was a winter morning when I had a casual talk with Professor Bob Grubbs in his office. He was so warm and welcoming and happily approved me to join his lab. This is Bob, who gives people unconditional support no matter who they are, or where they come from, to help them grow. This warm support makes me feel grateful every day at Caltech, and the warmth will be continued in the future. I'm also thankful to my co-advisor, Professor Brian Stoltz. I learned to be a synthetic chemist, from small details in weekly subgroups, to big ideas during conversation with him. Having both advisors was a unique experience. They both let me pursue my ideas and solve problems independently, and provided me great resources from both groups. I benefited not only from their guidance, but also from their wisdom. They are the advisors of my thesis, but also advisors in my life.

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I've spent five years in a wonderful group, and I've been overlapped with over 30 amazing people in this lab. I can't list them all but they all had a very significant impact on me. Zach Wickens was the first person I met from the Grubbs lab. I was impressed with his knowledge when he drew all the reactions he had done on a small piece of paper at a coffee shop. He mentored me in the beginning, and taught me all the basics as well as how to manage a research project. Crystal Chu was so lively and offered me lots of strategic advice. I also enjoyed lots of discussions with Choonwoo Lee. A new chapter of my graduate research didn't begin until Chen Xu joined the lab. She passed the torch to me to make me proud of being a synthetic chemist making complex natural products. In the meanwhile, I also learned a lot of metathesis from daily discussions with Tonia Ahmed.

The current group members made the Grubbs lab a wonderful place to work. Willie Wolf is a cool chemist and I'm so impressed with his understanding in kinetics. I really enjoyed the time we worked and hung out together. I will also not forget spending five years moving solvent boxes up with Chris Marotta. Yan Xu and I have similar backgrounds and

he shared so many past experiences with me. JK is a godsend and introduced me to potential postdoc opportunities, and I was always impressed by his energy and passion. Zainab Al-Saihati always brought us positive energy, and recently brought a baby to the world, and I wish her success in both family and career. I can still remember how happy Quan Gan was when I helped him set up his first column, and it was always fun to hang out with him. Jianchun Wang, Ki-Young Yoon, and Prof. Eunsung Lee just joined the group but I'm sure they will have a great experience in Grubbs lab.

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Hsi Lai Temple has a great Chinese community. Every time I went there it's like my second hometown. From meditation and Buddhism classes, I learned to be more calm and not to be attached to the transient emotions.

Thanks to my mom and dad. They never put high expectations on me, but always think about me from thousands of miles away. I'm grateful to their unconditional love and support that can never be paid back.

ABSTRACT

Prostaglandins are an important class of naturally occurring molecules which have multifaceted biological functions and widespread medical applications. Chapter 1 discusses the development of concise syntheses of four Δ^{12}-Prostaglandin J natural products, enabled by convergent stereoretentive cross-metathesis by Ru-based metathesis catalyst. Exceptional control of alkene geometry was achieved through stereoretention. Short syntheses (7–8 steps in longest linear sequences) were realized in a modular approach. An improved route using enzymatic resolution to obtain enantiopure 15d-PGJ_2 was also discussed.

Chapter 2 discusses a mild palladium-catalyzed aerobic intramolecular aminoacetoxylation method. Pyrrolidine and indoline derivatives were synthesized using molecular oxygen as oxidant mediated by catalytic NO_x species, which acts as an electron transfer mediator to access high-valent palladium intermediate as the presumed active oxidant.

Chapter 3 presents a new, robust synthesis of *gem*-dialkyl acyclic diene monomers with low-cost. Telechelic *gem*-dialkyl polyethylenes can be made by the metathesis polymerization of the *gem*-dialkyl acyclic diene monomers, followed by hydrogenation. These polymers feature low glass transition temperature and can be used as elastomers in the synthesis of polyurethanes and other block polymers.

PUBLISHED CONTENT AND CONTRIBUTIONS

Li, J.; Grubbs, R. H.; Stoltz, B. M. Palladium-Catalyzed Aerobic Intramolecular Aminoacetoxylation of Alkenes Enabled by Catalytic Nitrate. *Org. Lett*. **2016**, *18*, 5449–5451. doi: 10.1021/acs.orglett.6b02722.

J. L. led project design, experimental work, data acquisition and analysis, and manuscript preparation.

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J. L. led project design, experimental work, data acquisition and analysis, and manuscript preparation.

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NOMENCLATURE

$[\alpha]_D$	specific rotation at wavelength of sodium D line
°C	degrees Celsius
Å	Ångstrom
Ac	acetyl
Acac	acetylacetonate
AcOH	acetic acid
ADH	alcohol dehydrogenase
Adm	adamantyl
ALB	aluminum-lanthanum-BINOL complex
All	allyl
An	anisole
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1-binaphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
bp	boiling point
br	broad

Bu	butyl
Bz	benzoyl
c	concentration for specific rotation measurements (g/100 mL)
ca.	about (Latin circa)
calc'd	calculated
cat	catalytic
CDI	1,1'-carbonyldiimidazole
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethyl-cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DIBAL	diisobutylaluminum hydride
DIC	*N,N'*-Diisopropylcarbodiimide
DIFLUORPHOS	5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole

DIPEA	*N,N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N, N*′-Dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
dr	diastereomeric ratio
DTBM	di-*t*-butyl-methoxy
E	trans (entgegen) olefin geometry
e.g.	for example (Latin exempli gratia)
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI+	electron impact
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
FAB	fast atom bombardment
Fu	furanyl

g	gram(s)
G2	Grubbs catalyst 2nd generation
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)
HG-II	Hoveyda-Grubbs catalyst 2nd generation
hmim	2-methylimidazole
HMBC	heteronuclear multiple bond correlation
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide (HMPT)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	hertz
$h\nu$	light
i-	*iso*-
i-Pr	isopropyl
i.e.	that is (Latin id est)
IBX	2-iodoxybenzoic acid
IL-6	interleukin 6
IPA	isopropanol, 2-propanol
Ipc	diisopinocampheyl
IR	infrared (spectroscopy)
J	coupling constant
K	Kelvin(s) (absolute temperature)
kcal	kilocalorie
KP_i	potassium phosphate

L	liter; ligand
L*	chiral ligand
LDA	lithium diisopropylamide
LG	leaving group
lit.	literature value
LSB	lanthanum-sodium-BINOL
m	multiplet; milli
m	meta
M	metal; molar; molecular ion; Mega
m-CPBA	*meta*-chloroperoxybenzoic acid
m/z	mass to charge ratio
Me	methyl
mg	milligram(s)
min	minute(s)
MM	mixed method
MOC	methoxycarbonyl
mol	mole(s)
MOP	2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n	nano
N	normal
n-	*normal*-
NADP	nicotinamide adenine dinucleotide phosphate
Naph	naphthyl

NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
Pd/C	palladium on carbon
pen	pentyl
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline
Pin	2,3-dimethylbutane-2,3-diol (pinacol)
Piv	trimethylacetyl, pivaloyl
p*Ka*	p*K* for association of an acid
pmdba	bis(4-methoxybenzylidene)acetone
PMP	*para*-methoxy phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Proton sponge	1,8-bis(dimethylamino)naphthalene
Py	pyridine
q	quartet
R	generic for any atom or functional group
RCM	ring-closing metathesis
Ref.	reference
R_f	retention factor

RRCM	relay ring-closing metathesis
s	singlet
s-	*sec*-
sat.	saturated
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SFC	supercritical fluid chromatography
Solv	solvent
t	triplet
t-	*tert*-
T-Hydro	70% TBHP in water
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBD	1,3,4-triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine

TMS	trimethylsilyl
TMP	tetramethylpiperidine
TOF	time-of-flight
Tol	tolyl
t_R	retention time
TRAP	2,2"-bis[1 -(diphenylphosphino)ethyl]-1,1"-biferrocene
TRIS	tris(hydroxymethyl)aminomethane
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
v/v	volume to volume
Val	valine
w	weak
w/v	weight to volume
X	anionic ligand or halide
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
λ	wavelength
μ	micro
Z	cis (zusammen) olefin geometry