

DEVELOPMENT OF SYNTHETIC STRATEGIES FOR THE  
TOTAL SYNTHESIS OF *ENT*-KAURANOID AND DITERPENOID ALKALOID  
NATURAL PRODUCTS

Thesis by

Victor Wei-Dek Mak

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*To My Mother*

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## ABSTRACT

As part of an ongoing synthetic effort directed towards biologically active *ent*-kauranoid natural products, the preparation of two structurally unique natural products, (–)-trichorabdal A and (–)-longikaurin E, is presented. The syntheses intercept an early intermediate from the synthetic route towards the rearranged natural product (–)-maoecrystal Z, and thus, represents a unified synthetic strategy to access structurally unique *ent*-kauranoids. Specifically, the syntheses are enabled by a palladium-mediated oxidative cyclization of a silyl ketene acetal to install a key quaternary center within the bicyclo[3.2.1]octane unit, as well as a reductive cyclization of an aldehyde-lactone to construct the oxabicyclo[2.2.2]octane motif of (–)-longikaurin E.

A synthetic strategy to access C<sub>19</sub>-diterpenoid alkaloids, specifically of the *aconitine* type, is presented. These highly bridged polycyclic natural products are generally characterized by a substituted piperidyl ring bridging a hydrindane framework that is further attached to a bicyclo[3.2.1]octane. The synthetic strategy relies on the enantioselective synthesis of two bicyclic fragments, which are coupled in a convergent fashion through a 1,2-addition/semipinacol rearrangement sequence to forge a sterically hindered quaternary center. Efficient access to late stage intermediates has enabled the synthesis of the aconitine carbocyclic core, with appropriate functionality for advancement to a selective voltage-gated K<sup>+</sup> channel blocker, talatisamine. Additionally, the synthetic strategy described herein is well applicable to the synthesis of related *denudatine* and *napelline* type C<sub>20</sub>-diterpenoid alkaloids.



## PUBLISHED CONTENT AND CONTRIBUTIONS

Portions of the work described herein were disclosed in the following publications:

Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764.

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V.W.M. conducted experiments towards (–)-longikaurin E, and contributed to the preparation of the manuscripts and supporting information.

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**LIST OF ABBREVIATIONS**

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	para-acetamidobenzenesulfonyl azide
Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
<i>aq</i>	aqueous
Ar	aryl group
atm	atmosphere(s)
BINOL	1,1'-bi-2,2'-naphthol
bipy	2,2'-bipyridine
Bn	benzyl
Boc	tert-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	butyl or <i>norm</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
BQ	1,4-benzoquinone
Bz	benzoyl

c	concentration of sample for measurement of optical rotation
$^{13}\text{C}$	carbon-13 isotope
/C	supported on activated carbon charcoal
$^{\circ}\text{C}$	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
cat.	catalyst
Cbz	benzyloxycarbonyl
cf.	consult or compare to (Latin: confer)
<i>cis</i>	(zusammen) on the same side
$\text{cm}^{-1}$	wavenumber(s)
CoA	Coenzyme A
conc.	concentrated
conv.	conversion
Cp	cyclopentadienyl
CSA	camphor sulfonic acid
Cy	cyclohexyl
$\Delta$	heat or difference
$\delta$	chemical shift in ppm
d	doublet
d	deutero or dextrorotatory
D	deuterium
dba	dibenzylideneacetone

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
<i>de novo</i>	starting from the beginning; anew
DIPEA	<i>N,N</i> -diisopropylethylamine
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	<i>N,N</i> -dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
<i>ee</i>	enantiomeric excess
E	methyl carboxylate (CO <sub>2</sub> CH <sub>3</sub> )
E <sup>+</sup>	electrophile
<i>E</i>	trans (entgegen) olefin geometry
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
<i>e.g.</i>	for example (Latin: <i>exempli gratia</i> )



EI	electron impact
<i>ent</i>	enantiomer of
epi	epimeric
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
<i>et al.</i>	and others (Latin: <i>et alii</i> )
FAB	fast atom bombardment
FTIR	fourier transform infrared spectroscopy
g	gram(s)
h	hour(s)
<sup>1</sup> H	proton
[H]	reduction
HDA	hetero-Diels–Alder
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
hν	irradiation with light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC <sub>50</sub>	half maximal inhibitory concentration (50%)

<i>i.e.</i>	that is (Latin: <i>id est</i> )
iso	isomeric
<i>in situ</i>	in the reaction mixture
J	coupling constant in Hz
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LC/MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
m	multiplet or meter(s)
M	molar or molecular ion
<i>m</i>	meta
μ	micro
<i>m</i> -CPBA	meta-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)

MM	mixed method
mol	mole(s)
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
<i>m/z</i>	mass-to-charge ratio
NBS	<i>N</i> -bromosuccinimide
nd	not determined
NHC	<i>N</i> -heterocyclic carbene
nm	nanometer(s)
nM	nanomolar
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
NPh	naphthyl
Nu	nucleophile
<i>o</i>	ortho
[O]	oxidation
P	peak
<i>p</i>	para
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHAL	1,4-phthalazinediyl diether
PIFA	[bis(trifluoroacetoxy)iodo]benzene
Pin	pinacol
PivOH	pivalic acid
$pK_a$	acid dissociation constant
pm	picometer(s)
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	<i>isopropyl</i>
<i>n</i> -Pr	propyl or <i>norm</i> -propyl
psi	pounds per square inch
py	pyridine
PYR	2,5-diphenyl-4,6-pyrimidinediyl diether
q	quartet
QD	Quinidine
QN	Quinine
quant.	quantitative
R	generic (alkyl) group

RL	large group
R	rectus
RCM	ring-closing metathesis
recry.	recrystallization
ref	reference
Rf	retention factor
rgt.	reagent
rt	room temperature
s	singlet or seconds
sat.	saturated
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBME	<i>tert</i> -butyl methyl ether
TBS	<i>tert</i> -butyldimethylsilyl
TC	thiophene-2-carboxylate
temp	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight

tol	tolyl
TPAP	tetrapropylammonium perruthenate
<i>trans</i>	on the opposite side
Ts	para-toluenesulfonyl (tosyl)
UV	ultraviolet
<i>vide infra</i>	see below
w/v	weight per volume
X	anionic ligand or halide
xs	excess
Z	<i>cis</i> (zusammen) olefin geometry