A UNIFIED STRATEGY TO ENT-KAURANOID NATURAL PRODUCTS: TOTAL SYNTHESES OF (–)-MAOECRYSTAL Z, (–)-TRICHORABDAL A, AND (–)-LONGIKAURIN E

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To my teachers

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ABSTRACT

The diterpenoid constituents of the *Isodon* plants have attracted reasearchers interested in both their chemical structures and biological properties for more than a half-century. In recent years, the isolations of new members displaying previously unprecedented ring systems and highly selective biological properties have piqued interest from the synthetic community in this class of natural products.

Reported herein is the first total synthesis of such a recently isolated diterpenoid, (–)-maoecrystal Z. The principal transformations implemented in this synthesis include two highly diastereoselective radical cyclization reactions: a Sm^{II}-mediated reductive cascade cyclization, which forms two rings and establishes four new stereocenters in a single step, and a Ti^{III}-mediated reductive epoxide-acrylate coupling that yields a functionalized spirolactone product, which forms a core bicycle of maoecrystal Z.

The preparation of two additional *ent*-kauranoid natural products, (–)-trichorabdal A and (–)-longikaurin E, is also described from a derivative of this key spirolactone. These syntheses are additionally enabled by the palladium-mediated oxidative cyclization reaction of a silyl ketene acetal precursor that is used to install the bridgehead all-carbon quaternary stereocenter and bicyclo[3.2.1]octane present in each natural product. These studies have established a synthetic relationship among three architecturally distinct *ent*-kaurane diterpenoids and have forged a path for the preparation of interesting unnatural *ent*-kauranoid structural analogs for more thorough biological study.

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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
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl

C	cytosine
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
Cys	cysteine
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
EDC	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide
e.g.	for example (Latin: *exempli gratia*)

EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
ETP	epipolythiodiketopiperazine
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)

i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
m-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
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution

pK_a	acid dissociation constant
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
Pro	proline
psi	pounds per square inch
py	pyridine
pyr	pyridine
q	quartet
R	alkyl group
R	rectus
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
s	selectivity factor = $k_{\text{rel(fast/slow)}} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl

SOD	superoxide dismutase
Su	succinimide
t	triplet
T	thymine
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
Teoc	trimethylsilylethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl

Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry