I. SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF POLYCYCLIC NATURAL PRODUCTS – COMMUNESIN F, PEROPHORAMIDINE AND INELEGANOLIDE
II. NICKEL CATALYZED INTRAMOLECULAR C–O BOND FORMATION

Thesis by

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To my family,

for their unwavering support and dedication

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ABSTRACT

Expedient synthetic approaches to the highly functionalized polycyclic alkaloids communesin F and perophoramidine are described using a unified approach featuring a key decarboxylative allylic alkylation to access a crucial and highly congested 3,3-disubstituted oxindole. Described are two distinct, stereoselective alkylations that produce structures in divergent diastereomeric series possessing the critical vicinal all-carbon quaternary centers needed for each synthesis. Synthetic studies toward these challenging core structures have revealed a number of unanticipated modes of reactivity inherent to these complex alkaloid scaffolds. Finally, a previously unknown mild and efficient deprotection protocol for the *o*-nitrobenzyl group is disclosed – this serendipitous discovery permitted a concise endgame for the formal syntheses of both communesin F and perophoramidine.

In addition, the atroposelective synthesis of PINAP ligands has been accomplished via a palladium-catalyzed C–P coupling process through dynamic kinetic resolution. These catalytic conditions allow access to a wide variety of alkoxy- and benzyloxy-substituted PINAP ligands in high enantiomeric excess.

An efficient and exceptionally mild intramolecular nickel-catalyzed carbon–oxygen bond-forming reaction between vinyl halides and primary, secondary, and tertiary alcohols has been achieved. This operationally simple method allows direct access to cyclic vinyl ethers in high yields in a single step.

Finally, synthetic studies toward polycyclic ineleganolide are described. The entire fragmented carbon framework has been constructed from this work. Highly (Z)-selective olefination was achieved by the method by the Ando group.

PUBLISHED CONTENT AND CONTRIBUTIONS

1. Han, S.-J.; Vogt, F.; Krishnan, S.; May, J. A.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. A Diastereodivergent Synthetic Strategy for the Syntheses of Communesin F and Perophoramidine. *Org. Lett.* **2014**, *16*, 3316–3319. DOI: 10.1021/ol5013263.

Han, S.-J. participated in designing the synthesis, synthesized compounds, prepared the data, crystalized the key compounds and wrote the manuscript.

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3. Lee, C. W.; Han, S.-J.; Virgil, S. C.; Stoltz, B. M. Stereochemical evaluation of bis(phosphine) copper catalysts for the asymmetric alkylation of 3-bromooxindoles with α-arylated malonate esters. *Tetrahedron* **2015**, *71*, 3666–3670. DOI: 10.1016/j.tet.2014.10.065.

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LIST OF ABBREVIATIONS

Å	Ångstrom
λ	wavelength
μ	micro
μwaves	microwave irradiation
$[\alpha]_D$	specific rotation at wavelength of sodium D line
[H]	reduction
[O]	oxidation
°C	degrees Celsius
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
B3LYP	3-parameter hybrid Becke exchange/ Lee–Yang–Parr correlation functional
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	Bis(2-oxo-3-oxazolidinyl)phospinic
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
c	concentration for specific rotation measurements

ca.	about (Latin circa)
calc'd	calculated
CAN	cerium ammonium nitrate
cat	catalytic
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	compare (Latin confer)
CI	chemical ionization
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
Cp	cyclopentadienyl
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
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethyl azodicarboxylate
dec	decomposition
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DKR	dynamic kinetic resolution
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate

DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
e.g.	for example (Latin exempli gratia)
E_A	activation energy
EC_{50}	median effective concentration (50%)
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	enantiomeric excess
EI+	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)
$h\nu$	light
HBPin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane; pinacolborane
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol

HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
i.e.	that is (Latin id est)
IBX	2-iodoxybenzoic acid
IC_{50}	median inhibition concentration (50%)
IMDA	Intramolecular Diels–Alder reaction
IPA	isopropanol, 2-propanol
i-Pr	isopropyl
IR	infrared (spectroscopy)
IRC	intrinsic reaction coordinate
J	coupling constant
K	Kelvin(s) (absolute temperature)
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	liter; ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
lit.	literature value
m	multiplet; milli
m	meta
M	metal; molar; molecular ion
m/z	mass to charge ratio
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl

mg	milligram(s)
MHz	megahertz
min	minute(s)
MM	mixed method
MMPP	magnesium monoperoxyphthalate
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MVK	methyl vinyl ketone
n	nano
N	normal
nbd	norbornadiene
NBS	*N*-bromosuccinimide
n-Bu	butyl
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nosyl	nitrobenzenesulfonyl
Nu	nucleophile
o	ortho
OKR	oxidative kinetic resolution
p	para
PCC	pyridinium chlorochromate
Pd/C	palladium on carbon
PDC	pyridinium dichromate

Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline ligand
Piv	pivaloyl
p*Ka*	p*K* for association of an acid
PMB	*p*-methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTU	*n*-Propylthiouracil
Py	pyridine
q	quartet
R	generic for any atom or functional group
Ref.	reference
R_f	retention factor
s	singlet or strong or selectivity factor
sat.	saturated
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SEM	2-(trimethylsilyl)ethoxymethyl
SFC	supercritical fluid chromatography
S_N2	second-order nucleophilic substitution
S_N2'	nucleophilic substitution with allylic rearrangement
sp	sparteine
sp.	species
t	triplet
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
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
TOF	time-of-flight
Tol	tolyl
t_R	retention time
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
v/v	volume to volume
$VO(acac)_2$	vanadyl acetoacetonate
w	weak
w/v	weight to volume
X	anionic ligand or halide