PROGRESS TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF VARIECOLIN

AND

GAS-PHASE STUDIES OF THE TWISTED AMIDE 2-QUINUCLIDONE

Thesis by

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To my mother

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was intrigued by his labs that were a constant exercise in creativity, critical thinking, and fun.

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ABSTRACT

Biologically active natural products and pharmaceuticals often present intriguing structural features that can challenge the state of the art in catalysis and synthetic methodology for their preparation. The identification of unique targets thus stimulates the development of new strategies and methods for chemical synthesis. The complex architecture representative of the variecolin family of sesterterpenes has inspired our pursuit of new tactics that has enabled the expansion of methods from our laboratory.

First, progress toward the asymmetric total synthesis of variecolin is discussed. Our convergent synthetic approach bisects the target into two complex fragments to address the main structural challenges. A microwave-promoted tandem Wolff/Cope rearrangement of vinyl cyclobutyl diazocarbonyls has been developed that provides access to functionalized, fused eight-membered rings and is used to construct the central B ring of variecolin. In addition, the utility of our Pd-catalyzed enantioselective alkylation method is extended to a new vinylogous ester substrate class to produce a quaternary ketone in excellent yield with high selectivity that is an exceptional substrate for an efficient ring contraction to the cyclopentene D ring system. The successful asymmetric preparation of our two devised fragments has facilitated initial studies toward their coupling and completion of variecolin.

Second, a preliminary examination of the substrate scope for the asymmetric alkylation of the vinylogous β-ketoester substrate class is described. Derivatives that perturb substrate electronics display enhanced reactivity and selectivity, generating products with excellent selectivities and expanding the potential of this versatile class of substrates. Furthermore, their utility is underscored as the key enantioselective transformation en route to the synthesis of the sesquiterpenoid (+)-carissone.

Finally, gas-phase studies of the twisted amide 2-quinuclidone are described. Proton affinity experiments have quantified its high basicity, which is comparable to a tertiary amine. A gas-phase synthesis of 2-quinuclidione via elimination of water and subsequent fragmentation further highlight the unusual characteristics of extremely twisted amides.

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
Anal.	combustion elemental analysis
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
Bz	benzoyl
c	concentration for specific rotation measurements
°C	degrees Celsius
ca.	about (Latin circa)
calc'd	calculated

CAN	ceric ammonium nitrate
cat	catalytic
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	compare (Latin confer)
CI	chemical ionization
CID	collision-induced dissociation
cm^{-1}	wavenumber(s)
comp	complex
Cy	cyclohexyl
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
dec	decomposition
DIAD	diisopropyl azodicarboxylate
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	(deoxy)ribonucleic acid
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio

E_A	activation energy
EC_{50}	median effective concentration (50%)
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin exempli gratia)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)
HIV	human immunodeficiency virus
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSV	herpes simplex virus
$h\nu$	light
Hz	hertz
IC_{50}	median inhibition concentration (50%)
i.e.	that is (Latin id est)
IR	infrared (spectroscopy)

J	coupling constant
kcal	kilocalorie
KDA	potassium diisopropylamide
KHMDS	potassium hexamethyldisilazide
λ	wavelength
L	liter
LDA	lithium diisopropylamide
lit.	literature value
LTQ	linear trap quadrupole
m	multiplet; milli
m	meta
m/*z*	mass to charge ratio
M	metal; molar; molecular ion
Me	methyl
MHz	megahertz
μ	micro
μwaves	microwave irradiation
min	minute(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal
nbd	norbornadiene

NBS	*N*-bromosuccinimide
NIST	National Institute of Standards and Technology
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
[O]	oxidation
o	ortho
p	para
PA	proton affinity
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
PHOX	phosphinooxazoline
Piv	pivaloyl
p*Ka*	p*K* for association of an acid
PMB	*p*-methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
PPL	porcine pancreas lipase
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl

Py	pyridine
q	quartet
ref	reference
R	generic for any atom or functional group
R_f	retention factor
rt	room temperature
s	singlet or strong or selectivity factor
sat.	saturated
SET	single electron transfer
S_N2	second-order nucleophilic substitution
sp.	species
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCDI	1,1'-thiocarbonyldiimidazole
TCNE	tetracyanoethylene
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
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

TON	turnover number
t_R	retention time
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
v/*v*	volume to volume
w	weak
w/*v*	weight to volume
X	anionic ligand or halide