PROGRESS TOWARD THE CORTISTATIN A CARBOCYLIC CORE

AND

THE DEVELOPMENT OF THE CATALYTIC ENANTIOSELECTIVE ALKYLATION OF 3-HALOOXINDOLES

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To my parents

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ABSTRACT

Biologically active natural products often contain interesting and complex structural features and functionalities that make them attractive targets for synthetic chemists. As such, these natural products can serve as inspiration for the development of new reaction methodology.

Cortistatin A contains a unique rearranged steroidal core and possesses potent anti-angiogenic activity. These features have made cortistatin A the target of many synthetic efforts, including ours. The progress toward the synthesis of the cortistatin A carbocyclic core via an enyne-ene metathesis is discussed. Our studies towards the construction of the cortistatin A carbocyclic core yielded an interesting result, wherein an attempted S_N2 inversion of a secondary mesylate afforded product with retention of stereochemistry.

Oxindole derived motifs are also prevalent in biologically active molecules. More specifically, 3,3-disubstituted oxindoles can be used to access pyrrolidinylspirooxindole and pyrrolidinoindoline cores. Herein, the development of a catalytic enantioselective malonate alkylation of 3-halooxindoles to access enantiopure 3,3-disubstituted oxindoles is detailed. We then demonstrate that the enantiopure 3,3-disubstituted oxindoles derived from this novel transformation can be used towards the construction of pyrrolidinylspirooxindole and pyrrolidinoindoline cores.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
°C	degrees Celsius
calc'd	calculated
CAN	ceric ammonium nitrate

Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
2,6-DTBP	2,6-di-*tert*-butylphenol

ee	enantiomeric excess
E^+	electrophile
E	trans (entgegen) olefin geometry
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
h	hour(s)
^1H	proton
^2H	deuterium
^3H	tritium
[H]	reduction
HMDS	hexamethyldisilamide or hexamethyldisilazide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid

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
LDA	lithium diisopropylamide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
Me	methyl
mg	milligram(s)
MHz	megahertz
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
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline
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
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
ref	reference
R_f	retention factor
s	singlet or seconds
S	sinister
sat.	saturated
Su	succinimide
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBCHD	2,4,4,5-tetrabromo-2,5-cyclohexadienone
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
temp	temperature
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
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