TOTAL SYNTHESIS OF CYANTHIWIGIN NATURAL PRODUCTS VIA DOUBLE ASYMMETRIC CATALYTIC ALKYLATION

AND

INVESTIGATIONS INTO THE NATURE OF DOUBLE ASYMMETRIC PROCESSES

Thesis by

John Andrew Enquist, Jr.

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To my parents

ACKNOWLEDGEMENTS

Though a single thesis is often considered a personal endeavor, it is undeniable that scientific research requires the combined contributions of many different individuals. The work detailed in this thesis is no exception; it would not have been possible without the input, guidance, and support of a great many people.

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I also wish to thank Professor Jay Siegel for introducing me to synthesis. When I first enrolled in classes at UCSD as an undergraduate in the fall of 2000, I was

exceptionally apprehensive about taking organic chemistry at all. Professor Siegel's enthusiasm and teaching style allayed my fears completely. Rather than being overwhelming, his course was both an exciting and informative view into the field of synthetic chemistry. In his dedication to teaching, Professor Siegel held regular study sessions for his course on every Saturday afternoon. It was during these informal gatherings that I gained an appreciation for the science and an insight into its practical application that no textbook could cover. The subsequent classes taught by and advice that I received from Professor Siegel helped to shape my path toward graduate school, and I remain grateful for his influence.

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Over the past six years, I have shared lab space with a number of exceptional graduate students and postdoctoral scholars. When I first joined the group, JT Mohr was generous (or perhaps unwitting) enough to allow me to share his hood. Not only did he accommodate an awkward and inexperienced first year student (something which significantly reduced his functional space), he also took the time out to teach me the proper basics of synthetic technique. From running asymmetric catalysis reactions to

using VNMR, JT was an exceptional mentor. Additionally, JT had an incredible tolerance for references to old movies and obscure internet culture, and never once complained when I would yell in aggravation at an exceptionally long column (or "Kahn column," as they eventually came to be known). Though I only spent a few short months cohabitating with JT in a single fume hood, he taught me much about synthesis, characterization, and surviving graduate school. He was also an excellent friend, and continued to suffer my sense of humor for years after I finally vacated his space.

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most difficult of trials. My father has also been continually understanding and enthusiastic about my graduate studies. Weekly conversations with him always refueled my energy for the days ahead, and his advice on everything from doctors to cooking assisted me greatly. Unfortunately, a comprehensive list of all of the family members who have helped me in my graduate studies would be too large to include here. Instead, I would like to briefly offer my thanks to my stepfather Mike, my stepmother Janet, all of my grandparents, my stepbrothers Dave, Ryan, and Ben, my stepsisters Tracy, Tiffany, Christy, and Jenna, and all of their spouses and children. Their presence in my life has made me richer, and their belief in me has bolstered my resolve at times when I have needed it most.

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ABSTRACT

Since the initial isolation of the cyathane molecules in 1970, considerable synthetic interest has been invested into the preparation of these diterpenoid natural products. Owing to the biological activity and intriguing molecular architecture of these compounds, the members of the cyathane family of natural products have emerged as appealing targets for total synthesis. After a brief summary of the isolation and bioactivity properties of these diterpene compounds, previous synthetic efforts toward these molecules are reviewed.

A concise and versatile approach toward the preparation of the cyanthiwigin family of cyathane natural products is described. By leveraging a unique double asymmetric catalytic alkylation procedure it is possible to quickly establish two of the most critical stereocenters of the cyanthiwigin framework with high levels of selectivity and expediency. The synthesis additionally employs a tandem ring-opening and cross-metathesis reaction, and an aldehyde-olefin radical cyclization process, to rapidly arrive at the tricyclic cyathane core of the cyanthiwigin molecules. From this unifying intermediate, the preparation of cyanthiwigins B, F, and G are attained swiftly and without the need for protecting groups.

The nature of double asymmetric transformations is investigated from a historical, mathematical, and experimental perspective. The initial findings of Langenbeck and Horeau concerning the enantioenriching effects of scalemic duplication are described, with a specific focus on the impact of this phenomenon on total synthesis. A thorough mathematical examination, based on the work of Kagan, is then presented for situations involving double asymmetric transformations of prochiral starting materials. Expressions relating the final quantities of the stereoisomeric products to the intermediary selectivity of each stereoselective process are presented based on these formulae.

Finally, experiments designed to probe the selectivity of each stage of stereoselective bond construction in a double asymmetric process are presented. The compiled results are scrutinized in keeping with the previously derived equations, and these findings are analyzed to understand the nature of the double asymmetric processes in question.

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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
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bn	benzyl
Bz	benzoyl
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 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
CSA	camphor sulfonic acid
d	doublet
D	dextrorotatory
dba	dibenzylideneacetone
pmdba	bis(4-methoxybenzylidene)acetone
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane

DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HMDS	hexamethyldisilamide or hexamethyldisilazide
$h\nu$	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
min	minute(s)

mL	milliliter(s)
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
o	ortho
[O]	oxidation
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
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
r	selectivity = [major stereoisomer – minor stereoisomer]/[major stereoisomer + minor stereoisomer]
ref	reference
R_f	retention factor
s	singlet or seconds
s	selectivity factor = $k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl

temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
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	*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