# Forays into the Synthesis of Zoanthenol: Intriguing Patterns in Reactivity and Selectivity

Thesis by

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### DEDICATION

To my parents, Dave and Lucy Stockdill, who have sacrificed so much for me.

To my sister and brother, Teresa Barth and Jon Stockdill, who have been role models to me all of my life.

To my eighth grade science teacher, Mary Alice Robinson, who sparked a passion that has not died.

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...It is impossible to start....

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### ABSTRACT

The zoanthamine family of alkaloids has attracted the attention of synthetic chemists for over two decades, beginning with the first report of their isolation in 1984. Not only are these stereochemically dense polycyclic compounds structurally fascinating, but they also display interesting and important biological activities. Foremost among these is the potent anti-osteoporotic effect of norzoanthamine. To date, norzoanthamine remains the only member to have succumbed to total synthesis, by Miyashita and coworkers in 2004. Our studies began by targeting zoanthenol, a structurally similar natural product that possesses the key stereochemical challenges of norzoanthamine, while offering unique opportunities for strategic development as compared to the other family members.

The synthetic work described herein focuses on approaches to the tricyclic core of zoanthenol, specifically employing an approach by which the stereochemical complexity of the C ring, marked by the challenging vicinal all-carbon quaternary centers, is addressed early in the synthesis. These functionalized C ring synthons are then tethered to an aromatic A ring synthon, and methods to form the final bond of the B ring are explored. Special attention is given to the acid-mediated Friedel-Crafts cyclization approach. In addition to the acid-mediated cyclization approach, an alternative cyclization method is discussed wherein the A ring is substituted with a halogen in order to enable generation of a radical. This radical then undergoes a 1,4-addition into a fully substituted enone to close the B ring and provide the desired stereochemistry both of the two new stereocenters that are generated in the cyclization.

In these efforts, we have learned a great deal about the factors governing selectivity and reactivity in these systems. For each case, stereochemical models are discussed and key structural requirements for future investigations are outlined.

### PROLOGUE

### The Importance of Natural Products Synthesis

# This prologue is primarily for the benefit of readers outside of the field of chemistry, who may not be familiar with the nuances of the field of total synthesis, and thus, the impact of the research described in this thesis.

Natural products are complex molecules that have been isolated from a natural source, such as a tree bark, a fungus, a bacterial species, or even a marine creature. The study of natural products synthesis is essential to the advancement of organic chemistry, as well as to society as a whole. A natural product synthesis involves looking at a structure that has been isolated from nature, and then finding a way to make it from much smaller starting materials. As such, it is an ideal platform for the discovery of new reactions because every natural product presents a unique array of bonds that have likely not been made before. In order to make some of these bonds, new chemistry must be invented. These new reactions are typically applied to related molecules of varying levels of complexity, leading to the development of a new reaction methodology. Thus, total synthesis fuels the discovery of new methodology, while new methodology simultaneously allows for the completion of total syntheses.

The broader impact of these studies is realized largely through the pharmaceutical industry. Although pharmaceutical companies invest a great deal of time and money into their own research programs, they are generally very focused on a specific goal such as finding a drug for breast cancer. This is a large enough problem on its own that the company cannot invest their own man-hours into synthesizing natural products from scratch. Thus, they turn to academic groups for key information about what bonds were the most challenging to make and what disconnections lead to the shortest and most modular synthesis of a compound. Short syntheses are important to pharmaceutical companies because even if every step of a 30-step synthesis of a compound proceeds with 90% yield (this is not typical), the overall yield for the process is (.9)<sup>30</sup> or 4%. If the company is going to conduct testing on the compound, they cannot afford to waste 96% of their original materials. Thus, it is important for academic groups to discover as many different types of reactions and ways to disconnect natural products as possible. It is also important to have a modular synthesis, so that analog compounds can be made and tested. In many cases, the best pharmaceutical agents are modified versions of natural products. Natural products offer the great advantage of having already been compatible with at least one living system, the one from which they were isolated. If that creature was able to survive with this compound inside it, it is more likely that a human will be able to tolerate the compound than for a molecule that has been 100% designed. Some important drugs that are natural products or derivatives include the antibiotics penicillin and vancomycin, contraceptives (+)-norgestrel and  $17\alpha$ -ethynylestradiol, the antiinflammatory agent indomethacin, and the ovarian, breast, and small lung cancer drug paclitaxel (taxol).

The research presented herein centers around the synthesis of a marine alkaloid, zoanthenol, isolated off the coast of the Canary Islands from polyps of the genus *Zoanthus*. A number of very similar compounds were also isolated from the zoanthids, and they comprise a family of natural products called the zoanthamines. As a family, the zoanthamines offer a range of biological activities including inhibition of inflammation in mouse ears, cytotoxicity against murine leukemia cells, broad-spectrum antibacterial activity, and activity against human platelet aggregation. Perhaps the most exciting biological activity is the excellent anti-osteoporotic activity demonstrated by norzoanthamine. In ovarioectomized mice, a good model for post-menopausal osteoporosis, treatment with norzoanthamine hydrochloride prevented the loss of bone mass and strength. Additionally, bone strength can be restored in ovarioectomized mice

by treatment with norzoanthamine hydrochloride without any observed uterine atrophy, a side effect of treatment with 17 $\beta$ -estradiol, the current standard in this type of therapy. This difference points to the possibility of a different mechanism of action than estrogen therapy, making the zoanthamines an important family of natural products to target for synthesis.

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# LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
ACN	acetonitrile
Ad	adamantyl
add'n	addition
AIBN	2,2'-azobis( <i>iso</i> -butyronitrile)
app.	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere
В.	Bacillus
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
bm	broad multiplet
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
br	broad
BRSM	based on recovered starting material
bs	broad singlet
BSA	N,O-bis(trimethylsilyl)acetamide
Bu	butyl

<i>n</i> -Bu	<i>n</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
С	concentration for optical rotation measurement
<sup>13</sup> C	carbon 13, isotope
/C	supported on activated carbon
°C	degrees Celsius
cat.	catalytic
calc'd	calculated
CAM	ceric ammonium molybdate stain
CAN	ammonium cerium(IV) nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
c-Hex	cyclohexyl
comb.	combined
comp.	complex
CSA	camphorsulfonic acid
conv	conversion
COSY	correlation spectroscopy
Су	cyclohexyl
d	doublet, deuterium, diameter, or day(s)
Δ	heat
δ	chemical shift in parts per million
DA	Diels-Alder
dba	dibenzylideneacetone

xliv

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane or methylene chloride
DDQ	2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DEAD	diethyl azodicarboxylate
decomp.	decomposes
DIBAL	diisobutylaluminum hydride
DIBAL-H	diisobutylaluminum hydride
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4- bis(diphenylphosphino)butane
DIPA	diisopropyl amine
DIPEA	diisopropylethylamine
DMA	N,N-dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	3,5,3',5'-dimethoxydibenzylideneacetone
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	N,N'-dimethyl propylene urea
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppb	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane

dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DS.	Dean-Stark conditions
ee	enantiomeric excess
E	entgegen olefin geometry
Е.	Escherichia
EI	electrospray ionization
equiv	equivalent(s)
Et	ethyl
FAB	fast atom bombardment
g	gram
GC	gas chromatography
Grubbs II	Grubbs second-generation metathesis catalyst
[H]	reduction
h	hour(s) or height
h	
ΠV	light
¹H	light proton
иv <sup>1</sup> Н <sup>3</sup> Н	light proton tritium
пv <sup>1</sup> H <sup>3</sup> H HMBC	light proton tritium heteronuclear multiple bond correlation
<sup>1</sup> H <sup>3</sup> H HMBC HMDS	light proton tritium heteronuclear multiple bond correlation hexamethyldisilazide or hexamethyldisilizane
1V 1H 3H HMBC HMDS HMPA	light proton tritium heteronuclear multiple bond correlation hexamethyldisilazide or hexamethyldisilizane hexamethylphosphoramide
IV IH 3H HMBC HMDS HMPA HPLC	light proton tritium heteronuclear multiple bond correlation hexamethyldisilazide or hexamethyldisilizane hexamethylphosphoramide high-performance liquid chromatography
<sup>1</sup> H <sup>3</sup> H HMBC HMDS HMPA HPLC HRMS	light proton tritium heteronuclear multiple bond correlation hexamethyldisilazide or hexamethyldisilizane hexamethylphosphoramide high-performance liquid chromatography high-resolution mass spectroscopy
IV IH IH IH IMBC IMBC IMMDS IMPA IMPA IPLC IRMS ISQC	light proton tritium heteronuclear multiple bond correlation hexamethyldisilazide or hexamethyldisilizane hexamethylphosphoramide high-performance liquid chromatography high-resolution mass spectroscopy
IV IV IN IN IN IN IN IN IN IN IN IN IN IN IN	light proton tritium heteronuclear multiple bond correlation hexamethyldisilazide or hexamethyldisilizane hexamethylphosphoramide high-performance liquid chromatography high-resolution mass spectroscopy heteronuclear single quantum coherence hertz

X	V11

i	iso
IBX	2-iodoxybenzoic acid
IC <sub>50</sub>	concentration required for 50% growth inhibition
IL	interleukin
IMDA	intramolecular Diels-Alder
imid.	imidazole
Imid.	imidazole
IR	infrared spectroscopy
J	coupling constant
k	kilo
$k_{ m n}$	rate constant, n refers to various reactions, negative n indicates reverse reaction
kcal	kilocalories
KHMDS	potassium hexamethyldisilazide
L	liter
λ	wavelength
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LD <sub>50</sub>	Lethal Dosage to kill 50% of test population
LiHMDS	lithium hexamethyldisilazide
LITA	lithium tantalate
lut.	lutidine
m	meta
m	multiplet, meter, or milli
μ	micro
Μ	mega, metal, or molar

m/z	mass to charge ratio
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
( <i>R</i> , <i>R</i> )-Me-DUPHOS	(-)-1,2-Bis((2R,5R)-2,5- dimethylphospholano)benzene
MEK	methyl ethyl ketone
MH-60	mouse myelohybridoma cells
MIC	minimal inhibitory concetration
min	minute(s)
mol	mole(s)
mol%	percentage used based on moles
МОМ	methoxymethyl
( <i>R</i> )-MOP	(R)-(+)-2-(Diphenylphosphino)-2'-methoxy-1,1'- binaphthyl
mp or m.p.	melting point
Ms	methanesulfonyl
MS	molecular sieves
M.S.	molecular sieves
МТРА	$\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid
MVK	methyl vinyl ketone
Ν	normal
n	normal
n	nano
NBS	N-bromosuccinimide
NMP	N-methylpyrrolidinone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect

xlviii

NOESY	2D nuclear Overhauser effect spectroscopy
NR	no reaction
0	ortho
[0]	oxidation
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	prostoglandin
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
РНОХ	phosphinooxazoline
Phth	phthalamidyl
Piv	pivaloyl
РМА	phorbol myristate acetate
PMB	<i>p</i> -methoxybenzyl
PMBM	<i>p</i> -methoxybenzyloxymethyl
<i>p.o.</i>	administered orally
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl
psi	pounds per square inch
Py, py or Pyr	pyridine
q	quartet

QUINAP	( <i>R</i> )-(+)-1-(2-diphenylphosphino-1- naphthyl)isoquinoline
R	alkyl group
R	rectus (configurational)
Rearr.	Rearrangement
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
$R_f$	retention factor
RNA	ribonucleic acid
ROESY	rotational nuclear Overhauser effect spectroscopy
S	singlet
S	sinister (configurational)
<i>S</i> .	Salmonella or Staphylococcus
SAE	Sharpless asymmetric epoxidation
SAR	structure activity relationship
sat.	saturated
sept.	septet
S <sub>N</sub> '	allylic nucleophilic substitution
S <sub>N</sub> 1	unimolecular nucleophilic substitution
S <sub>N</sub> 2	bimolecular nucleophilic substitution
sp.	species
stoich.	stoichiometric
t	triplet
t	tertiary
t <sub>1/2</sub>	half-life
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
temp	temperature
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
ТРАР	tetrapropylammonium perruthenate
TROC	trichloroethoxycarbonyl
Ts	p-toluenesulfonyl or $p$ -toluenesulfonic
UV	ultraviolet
Vis	visual wavelength
v/v	volume per volume
wt%	percent by weight
w/v	weight per volume
X	halide or trifluoromethanesulfonate
Ζ	zusammen olefin geometry