PROGRESS TOWARD THE SYNTHESIS OF (+)-ZOANTHENOL

AND

THE DEVELOPMENT OF AN ASYMMETRIC TSUJI ALLYLATION REACTION

Thesis by

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To my parents

for their constant support

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perspective in science and his belief in my abilities. Dewey was tremendously important in my decision to go to graduate school, and my decision to work for Brian was in no small part due to their many similarities. As a chemist at the bench, I was fortunate to learn much from a true master, Professor Predrag Cudic, then a postdoc in the McCafferty group.

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ABSTRACT

The stereoselective synthesis of all carbon quaternary stereocenters is an important problem in synthetic chemistry due to their common occurrence in bioactive compounds. The zoanthamine class of marine natural products highlights the challenge in constructing such stereocenters. After a summary of the isolation, structure determination, and biological activities of the zoanthamine natural products, published approaches toward their chemical synthesis are reviewed.

Synthetic strategies toward the carbocyclic portion of zoanthenol focus on the synthesis of the three challenging quaternary stereocenters located on the central C ring. An unusual acid-mediated S_N' cyclization of a nucleophilic arene with an allylic alcohol forms the B ring and diastereoselectively constructs the benzylic C(12) quaternary stereocenter. However, difficulties with late-stage installation of the remaining C(9) quaternary stereocenter compelled the use of C ring synthons containing the vicinal C(9) and C(22) stereocenters installed at an early stage in the synthesis. Desymmetrization of a *meso*-anhydride containing vicinal quaternary stereocenters accomplishes this goal in an enantioselective fashion. Several C ring synthons bearing the vicinal quaternary stereocenters are elaborated with A ring fragments, and several methods for the formation of the C(11)-C(12) bond in these systems are explored. Ultimately, a radical conjugate addition strategy provides the carbocyclic core of zoanthenol with the correct relative configuration of all three quaternary stereocenters.

These efforts toward the synthesis of zoanthenol highlight the difficulty in generating enantioenriched α-quaternary cycloalkanones derived from ketones with multiple acidic α-hydrogens. The first direct catalytic enantioselective access to such products is achieved by the application of chiral bidentate phosphinooxazoline (PHOX) ligands to Tsuji's non-enantioselective allylation reactions. Cyclic allyl enol carbonates, silyl enol ethers, and allyl β-ketoesters all provide uniformly excellent yields and high enantioselectivity in the reaction. The limitations on the substrate scope of the reaction are discussed. Preliminary studies into the mechanism of these allylation reactions with prochiral enolate fragments suggest that they occur by a different mechanism than the outer-sphere nucleophilic attack commonly proposed in the alkylation of prochiral allyl fragments.

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List of Abbreviations

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
ACN	acetonitrile
Ad	adamantyl
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
br	broad
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for optical rotation measurement

^{13}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
comp	complex
CSA	camphorsulfonic acid
conv	conversion
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane or methylene chloride
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPA	diisopropyl amine

DMA	N,N’-dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	3,5,3’,5’-dimethoxydibenzylideneacetone
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
dr	diastereomeric ratio
ee	enantiomeric excess
E	entgegen olefin geometry
EI	electrospray ionization
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	gram
GC	gas chromatography
Grubbs II	Grubbs’ second generation metathesis catalyst

[H]	reduction
h	hour(s)
hν	light
^{1}H	proton
^{3}H	tritium
HMDS	hexamethyldisilazide or hexamethyldisilizane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
η^n	eta; n = number of atoms coordinated to metal
IC_{50}	concentration required for 50% growth inhibition
imid.	imidazole
IR	infrared spectroscopy
J	coupling constant
k_n	rate constant, n refers to various reactions, negative n indicates reverse reaction
kcal	kilocalories
KHMDS	potassium hexamethyldisilazide
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LD_{50}	Lethal Dosage to kill 50% of test population
LiHMDS	lithium hexamethyldisilazide

m	meta
m	multiplet or milli
μ	micro
M	mega, metal, or molar
m/*z*	mass to charge ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
(*R*,*R*)-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
MOM	methoxymethyl
(*R*)-MOP	(R)-(+)-2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MVK	methyl vinyl ketone
N	normal

NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	ortho
[O]	oxidation
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	prostaglandin
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Ph-H	benzene
PHOX	phosphinooxazoline
Phth	phthalamidyl
Piv	pivaloyl
PMA	phorbol myristate acetate
PMB	*p*-methoxybenzyl
PMBM	*p*-methoxybenzyloxymethyl
p.o.	administered orally
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl

psi	pounds per square inch
Py or Pyr	pyridine
q	quartet
QUINAP	(R)-(+)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
R	alkyl group
R	rectus (configurational)
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
RNA	ribonucleic acid
s	singlet
S	sinister (configurational)
SAR	structure-activity relationship
sat.	saturated
stoich.	stoichiometric
t	triplet
TBAF	tetrabutylammonium fluoride
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
TPAP	tetrapropylammonium perruthenate
TROC	trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl or *p*-toluenesulfonic
UV	ultraviolet
Vis	visual wavelength
v/v	volume per volume
w/v	weight per volume
X	halide or trifluoromethanesulfonate
Z	zusammen olefin geometry