

STUDIES TOWARD THE TOTAL SYNTHESIS OF RITTERAZINE B: THE
INVESTIGATION OF ALKYNYLATION REACTIONS FOR USE IN THE
SYNTHESIS OF THE WESTERN FRAGMENT

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ABSTRACT

The ritterazine and cephalostatin natural products have biological activities and structures that are interesting to synthetic organic chemists. These products have been found to exhibit significant cytotoxicity against P388 murine leukemia cells, and therefore have the potential to be used as anticancer drugs. The ritterazines and cephalostatins are steroidal dimers joined by a central pyrazine ring. Given that the steroid halves are unsymmetrical and highly oxygenated, there are several challenges in synthesizing these compounds in an organic laboratory.

Ritterazine B is the most potent derivative in the ritterazine family. Its biological activity is comparable to drugs that are being used to treat cancer today. For this reason, and the fact that there are no reported syntheses of ritterazine B to date, our lab set out to synthesize this natural product.

Herein, efforts toward the synthesis of the western fragment of ritterazine B are described. Two different routes are explored to access a common intermediate. An alkyne conjugate addition reaction was initially investigated due to the success of this key reaction in the synthesis of the eastern fragment. However, it has been found that a propargylation reaction has greater reactivity and yields, and has the potential to reduce the step count of the synthesis of the western fragment of ritterazine B.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
<i>p</i> -ABSA	<i>para</i> -acetamidobenzenesulfonyl azide
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol (“ <u>b</u> utylated <u>h</u> ydroxy <u>t</u> oluene”)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bp	boiling point
br	broad
Bu	butyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	butyl or <i>norm</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
C	cytosine

<i>c</i>	concentration of sample for measurement of optical rotation
¹³ C	carbon-13 isotope
¹⁴ C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: <i>confer</i>)
cm ⁻¹	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
Cys	cysteine
CSA	camphor sulfonic acid
d	doublet
<i>d</i>	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCE	1,2-dichloroethane
<i>de</i>	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylhexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
<i>ee</i>	enantiomeric excess
E	methyl carboxylate (CO ₂ CH ₃)
E ⁺	electrophile
<i>E</i>	trans (entgegen) olefin geometry
EC ₅₀	median effective concentration (50%)
EDC	<i>N</i> -ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide
e.g.	for example (Latin: <i>exempli gratia</i>)
EI	electron ionization

eq	equation
ESI	electrospray ionization
Et	ethyl
<i>et al.</i>	and others (Latin: <i>et alii</i>)
ETP	epipolythiodiketopiperazine
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
¹ H	proton
² H	deuterium
³ H	tritium
[H]	reduction
HATU	2-(7-aza-1 <i>H</i> -benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
<i>hν</i>	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC ₅₀	half maximal inhibitory concentration (50%)
<i>i.e.</i>	that is (Latin: <i>id est</i>)

IR	infrared spectroscopy
<i>J</i>	coupling constant
<i>k</i>	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
<i>l</i>	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
<i>m</i>	meta
μ	micro
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
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	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu ⁻	nucleophile
<i>o</i>	ortho
[O]	oxidation
<i>t</i> -Oct	<i>tert</i> -octyl (1,1,3,3-tetramethylbutyl)
<i>p</i>	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
pK_a	acid dissociation constant

PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl
<i>n</i> -Pr	propyl or <i>norm</i> -propyl
Pro	proline
psi	pounds per square inch
py	pyridine
pyr	pyridine
q	quartet
R	alkyl group
<i>R</i>	rectus
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
s	selectivity factor = $k_{\text{rel}(\text{fast/slow})} = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$, where C = conversion
<i>S</i>	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase

Su	succinimide
t	triplet
T	thymine
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
Teoc	trimethylsilylethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Troc	2,2,2-trichloroethoxycarbonyl

Ts	<i>para</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry