

THE FIRST TOTAL SYNTHESIS OF (-)-LEMONOMYCIN  
AND  
PROGRESS TOWARD THE TOTAL SYNTHESIS OF (+)-CYANOCYCLINE A

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*To the wonderful people who support me*

*and the great minds that taught me*

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## ABSTRACT

The first total synthesis of (–)-lemonomycin has been accomplished in an efficient and convergent manner. The synthesis features a highly diastereoselective, auxiliary-controlled dipolar cycloaddition that forms the bicyclic core and set the absolute stereochemistry of the natural product. The resulting diazabicyclic was advanced by Suzuki coupling, diastereoselective hydrogenation, and a highly convergent, completely diastereoselective Pictet-Spengler cyclization with a glycosyloxy-acetaldehyde. The Pictet-Spengler product was then converted to (–)-lemonomycin in three steps. The glycosyl portion of lemonomycin was synthesized diastereoselectively from D-threonine.

The synthesis of (+)-cyanocycline A has been approached along two synthetic routes. Progress along a silyl ether route led to the discovery of a new diastereoselective hydrogenation of an unsaturated diazabicyclic to set the C(4) stereochemistry of cyanocycline A. The product of this reduction was advanced through a convergent Stille coupling reaction to an enamide that contains all but six of the heavy atoms of cyanocycline A with the correct stereochemistry at each of the stereogenic carbons. Further, the enamide functionality is an ideal precursor for installation of the C(13b) amino group.

Progress along an oxazoline route has led to the development of a novel dipolar cycloaddition of an alkynyl oxazoline. The resulting diazabicyclic was advanced through a convergent Stille coupling reaction and diastereoselective hydrogenation to a late stage intermediate that contains all but three of the heavy atoms of cyanocycline A and has the correct relative stereochemistry for cyanocycline A.

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## LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation a wavelength of sodium D line
A	adenine
Ac	acetyl
ACN	acetonitrile
Ala	alanine
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol
Bn	benzyl
BOC	<i>tert</i> -butoxycarbonyl
BOM	benzyloxymethyl
br	broad
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
Bu	butyl
<i>n</i> -Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
<i>c</i>	concentration for optical rotation measurement
$^{13}\text{C}$	carbon 13, isotope

/C	supported on activated carbon
°C	degrees Celsius
calc'd	calculated
CAM	ceric ammonium molybdate stain
CAN	ammonium cerium(IV) nitrate
CBZ	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
C	cytosine
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
d	doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide

DNA	deoxyribonucleic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
<i>E</i>	entgegen olefin geometry
EI	electrospray ionization
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	gram
G	guanine
Gly	glycine
[H]	reduction
h	hour(s)
<sup>1</sup> H	proton
<sup>3</sup> H	tritium
HETCOR	heteronuclear correlation ( <sup>1</sup> H- <sup>13</sup> C)
HMDS	hexamethyldisilazide or hexamethyldisilazane
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy

Hz	hertz
IC <sub>50</sub>	concentration required for 50% growth inhibition
IR	infrared spectroscopy
<i>J</i>	coupling constant
kcal	kilocalories
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
L	liter
LUMO	lowest unoccupied molecular orbital
<i>m</i>	meta
m	multiplet or milli
μ	micro
M	mega
<i>m/z</i>	charge to mass ratio
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
MIC	minimal inhibitory concentration
min	minute(s)
M	metal of molar
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves

NBS	<i>N</i> -bromosuccinimide
NMO	4-methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
<i>o</i>	ortho
[O]	oxidation
<i>p</i>	para
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
ppm	parts per million
Pr	propyl
<i>i</i> -Pr	isopropyl
psi	pounds per square inch
pyr	pyridine
q	quartet
R	alkyl group
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R <sub>F</sub>	retention factor
RNA	ribonucleic acid
s	singlet
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenyl silyl

TBS	<i>tert</i> -butyldimethylsilyl
temp	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TROC	trichloroethoxycarbonyl
t	triplet
T	thymine
Ts	<i>p</i> -toluenesulfonyl
UV	ultraviolet
Vis	visual wavelength
v/v	volume per volume
w/v	weight per volume
X	halide or trifluoromethanesulfonate
Z	zusammen olefin geometry