CONVERGENT METHODS FOR SYNTHESIZING RINGS IN THE CONTEXT OF NATURAL PRODUCT SYNTHESIS:

I. Development of a Tandem Stille-Oxa-Electrocyclization Reaction, and Progress Toward the Total Synthesis of Saudin

II. Development of the Direct Acyl-Alkylation of Arynes, and its Application Toward the Total Synthesis of Amurensinine

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Uttam Krishan Tambar

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To my big brother

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This is by far the most important part of my thesis. Synthetic chemists often define their achievements in terms of the number of natural products they have made or the number of novel reactions they have developed. Yet, I realize that my greatest achievements have been the professional and personal relationships I have developed that have gotten me to this stage in life. So it is with tremendous gratitude that I write these acknowledgements to show my appreciation to some of the people who have helped me throughout the years.

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ABSTRACT

Cyclic molecular structures are ubiquitous in chemistry. Efficient and convergent methods to synthesize these rings are of great importance, specifically in the context of natural product synthesis. The development of two methods for the synthesis of the core structures of the natural products saudin and amurensinine are described.

First, the development of the tandem Stille-oxa-electrocyclization will be discussed in the context of synthetic efforts with saudin. The labdane diterpenoid saudin was isolated in 1985 by Mossa and Cassady from the leaves of the *Clutia richardiana (L.)* family *Euphorbiaceae*. The natural product was found to induce hypoglycemia in mice and therefore could be an appealing lead structure for the development of new agents to treat diabetes. A diastereoselective tandem Stille-oxa-electrocyclization reaction has been developed, which provides access to the core structure of saudin in a rapid and convergent manner. Additionally, this new reaction has been extended to the convergent preparation of related polycyclic pyran systems. Progress has been made on the advancement of these complex pyran systems toward the synthesis of saudin.

Secondly, the development of the direct acyl-alkylation of arynes will be described in the context of the total synthesis of the isopavine natural product amurensinine. The isopavine alkaloids are promising lead structures for the treatment of neuronal disorders such as as Parkinson's disease, Down's syndrome, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's chorea. All members of this family of natural products contain a seven-membered benzannulated carbocycle. To address the challenge of synthesizing the isopavines, an efficient and mild acyl-alkylation of arynes has been developed. The method forms *ortho*-disubstituted aromatic products that would otherwise be difficult to synthesize. Additionally, the method is used to synthesize medium-sized benzannulated carbocycles, such as the seven-membered ring structure in the isopavine alkaloids, by the ring-expansion of cyclic β-ketoesters. Overall, the transformation results in the formation of two new C–C bonds by the net insertion of an aryne into the α,β C-C σ-bond of a β-ketoester. This reaction has been applied in the total synthesis of amurensinine.

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LIST OF ABBREVIATIONS

p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl, acetate
AIBN	2,2'-azobisisobutyronitrile
app.	apparent
aq.	aqueous
atm	atmosphere
Bn	benzyl
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
°C	degrees Celsius
calc'd	calculated
CCDC	Cambridge Crystallographic Data Centre
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
ee	enantiomeric excess
equiv	equivalent
EI	electrospray ionization
Et	ethyl

FAB	fast atom bombardment
g	gram(s)
h	hour(s)
η^3	trihapto
[H]	reduction
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
hν	light
Hz	hertz
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
L	liter
m	multiplet or milli
m	meta
m/*z*	mass to charge ratio
μ	micro
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
nbd	norbornadiene
NMP	N-methylpyrrolidinone
NMR	nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
[O]	oxidation
*t*OcNC	*tert*-octyl isocyanide

p	para
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
ppm	parts per million
Pr	propyl
i-Pr	*iso*-propyl
pyr	pyridine
q	quartet
rt	room temperature
R_F	retention factor
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet