APPLICATION OF IMINIUM ACTIVATION TECHNOLOGIES TO NATURAL PRODUCT SYNTHESIS:

Total Syntheses of the Spiculisporic Acids, Progress Towards the Total Synthesis of Cylindrocyclophane F, and Formal Synthesis of Cylindrocyclophane A.

Thesis by

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ABSTRACT

The first enantioselective, catalytic vinylogous Mukaiyama-Michael reaction of siloxyfurans with simple α,β-unsaturated aldehydes has been reported using chiral imidazolidinones. This methodology provides access to enantioenriched γ-butenolides, a privileged motif in organic synthesis. The utility of this organocatalytic Mukaiyama-Michael reaction was highlighted by the total syntheses of (–)-spiculisporic acid and (–)-5-*epi*-spiculisporic acid.

Investigations into the total syntheses of cylindrocyclophanes A and F necessitated the development of a novel *B*-alkyl Suzuki cross-coupling of trimethylanilinium salts using a nickel(0) catalyst and bulky phosphine ligand. This methodology study revealed a very competitive nickel-catalyzed demethylation pathway, which produced dimethylaniline byproducts. A possible explanation for this side reaction is discussed. This technology was applied to a dimerization strategy for the C_2-symmetric cylindrocyclophane F. Synthesis of a dimerization precursor included an enantioselective organocatalytic 1,4-addition of 3,5-dimethoxy-*N,N*-dimethylaniline into an α,β-unsaturated aldehyde. However, the *B*-alkyl Suzuki cross-coupling was unsuccessful in promoting a dimerization.

Next, the synthesis of cylindrocyclophane A was explored using an alternative ring-closing metathesis dimerization strategy. A dimerization precursor was to be assembled via the cross-coupling of trimethylanilinium salts with potassium (vinyl)trifluoroborate salts, whose syntheses featured an organocatalytic 1,4-conjugate reduction of a α,β-disubstituted enal. This cross-coupling strategy revealed olefin isomerization as a major

side-reaction in the nickel-catalyzed Suzuki dimerization, making this route a non-productive approach to the natural product.

Lastly, formal synthesis of cylindrocyclophane A was accomplished using (i) a nickel-catalyzed Stille cross-coupling of an activated vinyl stannane with a judiciously chosen trimethylanilinium salt and (ii) an asymmetric palladium-catalyzed allylic alkylation of an acyclic ketone. The latter represents the first example of application of the $Pd_2(dba)_3$/*t*-Bu-PHOX catalyst system to effect an asymmetric allylic alkylation on an acyclic system with good stereoselectivity. This route constituted a formal synthesis of cyclindrocyclophane A in eight linear steps, making it more efficient than the published route to the same advanced intermediate reported by Smith, which was synthesized in eleven steps.

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ABBREVIATIONS

acac	acetylacetonate
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
AIBN	azabisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyl carbamate
BOM	benzyloxymethyl
BOM-Cl	benzyloxymethyl chloride
Bpin	pinacolatoboron
BPS	*tert*-butyldiphenylsilyl
Bz	benzoyl
Bu	butyl
COD	cyclooctadiene
Cp*	pentamethylcyclopentadiene
dba	dibenzylideneacetone
DCA	dichloroacetic acid
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIP-Cl	*B*-chlorodiisopinocampheylborane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNBA	2,4-dinitrobenzoic acid

dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphine)propane
EtOAc	ethyl acetate
GC	gas chromatography
Glu	glucosyl
h	hour
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
IC_{50}	concentration necessary for 50% inhibition
IMes • HCl	1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride
imid	imidazole
$IpcBH_2$	isopinocamphenylborane
IPr • HCl	1,3-bis(2,6-diisopropylphenyl)imidazolium chloride
LA	Lewis acid
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine amide
LUMO	lowest unoccupied molecular orbital
MCA	monochloroacetic acid
MeOH	methanol
MeOTf	methyl trifluoromethanesulfonate
min	minutes
MOM	methoxymethyl
NADH	nicotinamide adenine dinucleotide
NBA	2-nitrobenzoic acid
NMO	*N*-methylmorpholine-4-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

Nu	nucleophile
OBBD	10-bora-9-oxabicyclo[3.3.2]decane
PCy_3	tricyclohexylphosphine
PHOX	phosphinooxazoline
Piv	trimethylacetyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PT	5-phenyltetrazole
***p*-TSA**	*para*-toluenesulfonic acid
Pyr	pyridine
R_L	R_{LARGE}
R_S	R_{SMALL}
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
RCM	ring-closing metathesis
SAEP	(*S*)-1-amino-2-(1-ethyl-1-ethoxypropyl)pyrrolidine
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
SAPP	(*S*)-1-amino-2-(1-propyl-1-ethoxypropyl)pyrrolidine
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butylchlorodiphenylsilane
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butylchlorodimethylsilane
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TCA	trichloroacetic acid
TES	triethylsilyl
TESCl	chlorotriethylsilane
TFA	trifluoroacetic acid

TFE	2,2,2-trifluoroethanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TPAP	tetrapropylammonium perruthenate
$\mathbf{X_C}$	chiral auxiliary

To Mom