Collective Synthesis of Natural Products by Means of Organocascade Catalysis

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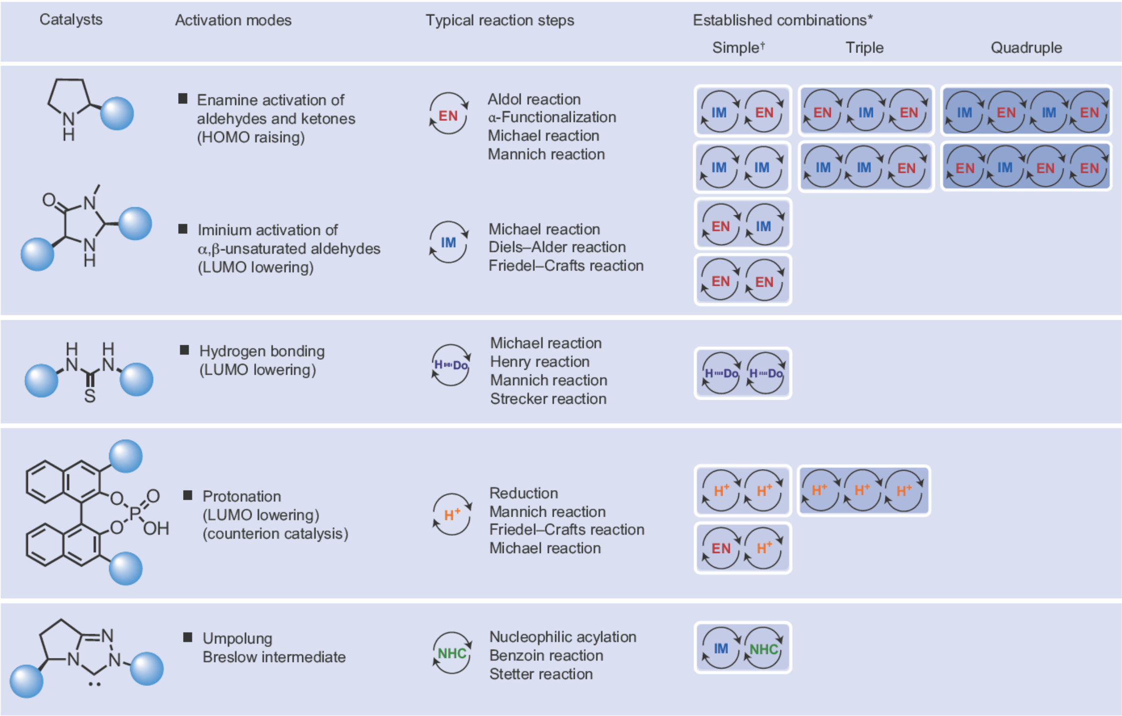
Nature **2011**, 475, 183

Nate Ware, Wipf Group Current Literature 08/06/11

Organocascade Catalysis

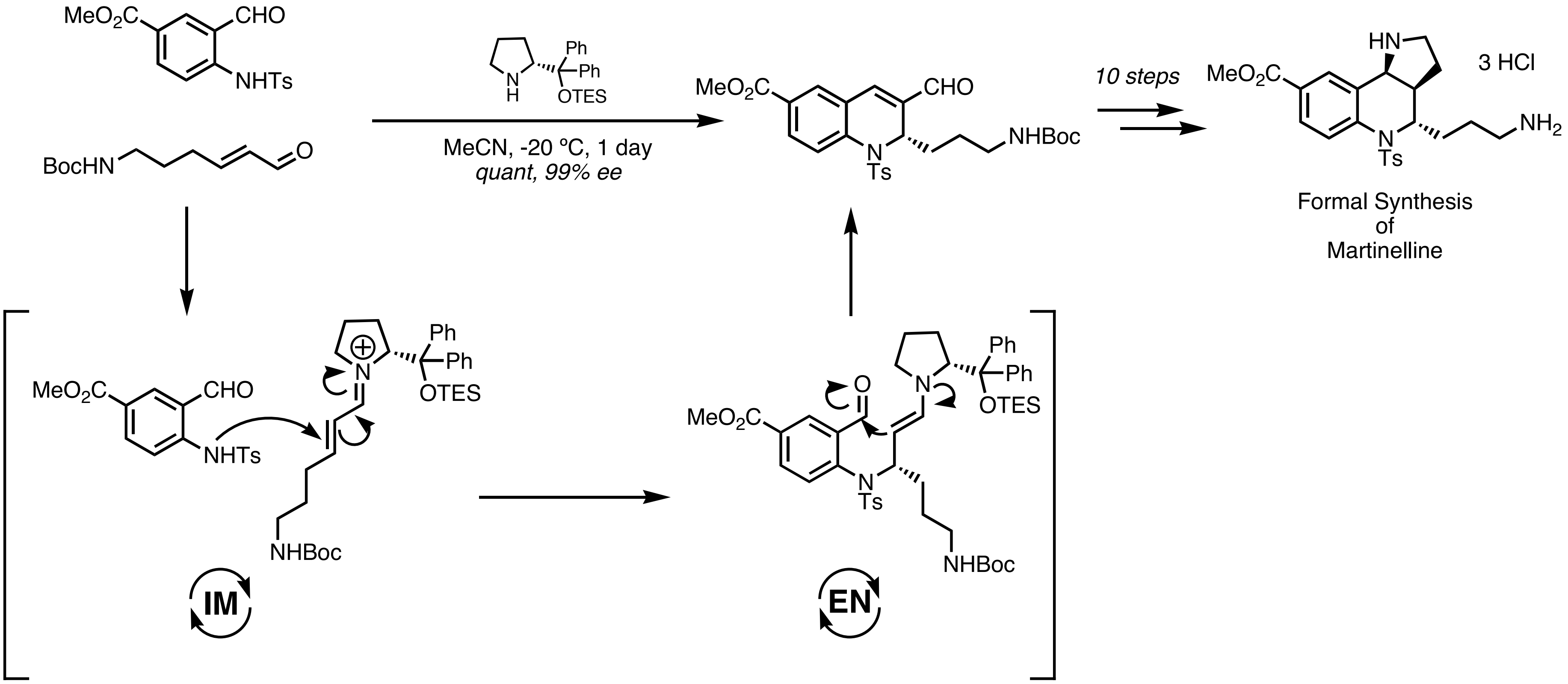
- Follows the “blueprints of biosynthesis”
  - cascade reaction sequences
  - avoidance of protecting groups
  - molecular complexity is built quickly and efficiently using simple key building blocks



Catalysts	Activation modes	Typical reaction steps		Established combinations*		
				Simple†	Triple	Quadruple
	■ Enamine activation of aldehydes and ketones (HOMO raising)	EN	Aldol reaction α-Functionalization Michael reaction Mannich reaction	IM EN IM IM EN IM EN EN	EN IM EN IM IM EN	IM EN IM EN EN IM EN EN
	■ Iminium activation of α,β-unsaturated aldehydes (LUMO lowering)	IM	Michael reaction Diels–Alder reaction Friedel–Crafts reaction			
	■ Hydrogen bonding (LUMO lowering)	H⋯Do	Michael reaction Henry reaction Mannich reaction Strecker reaction	H⋯Do H⋯Do		
	■ Protonation (LUMO lowering) (counterion catalysis)	H^+	Reduction Mannich reaction Friedel–Crafts reaction Michael reaction	H^+ H^+ EN H^+	H^+ H^+ H^+	
	■ Umpolung Breslow intermediate	NHC	Nucleophilic acylation Benzoin reaction Stetter reaction	IM NHC		

C. Grondal, M. Jeanty, D. Enders *Nature Chem.* **2010**, 2, 167
D. Enders, C. Grondal, M. Huttl, *ACIE*, **2007**, 46, 1570

Imine/Enamine Tandem Cascade



MeCN, -20 ºC, 1 day

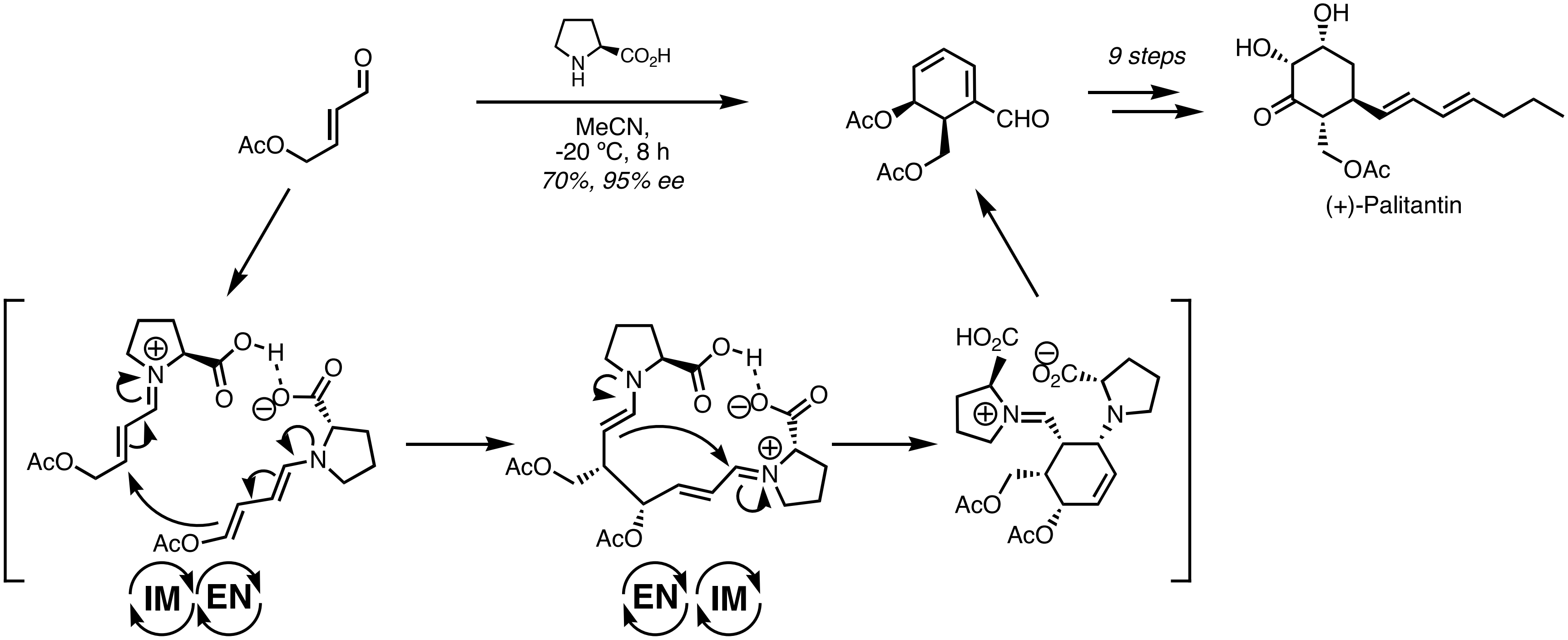
quant, 99% ee

10 steps

Formal Synthesis
of
Martinelline

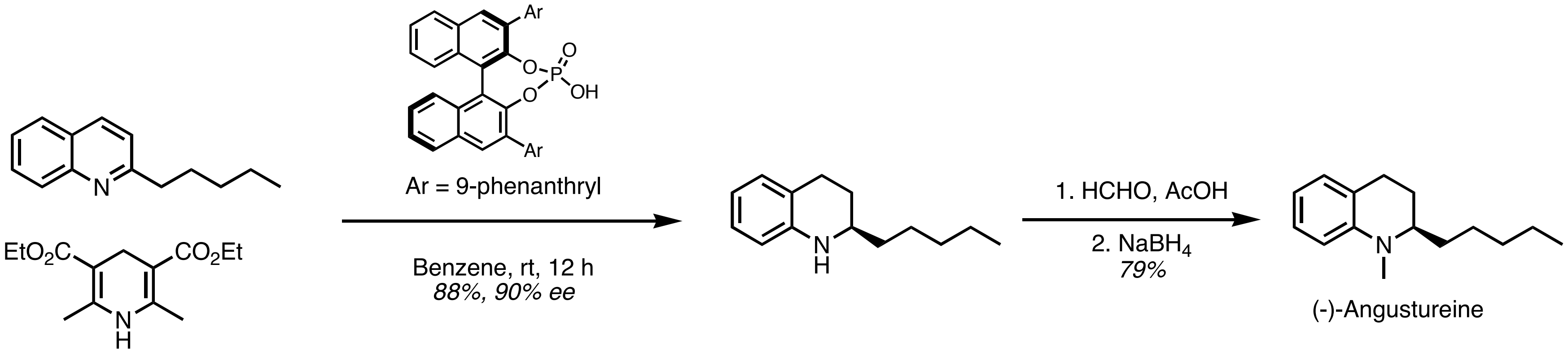
Y. Yoshitomi, H. Arai, K. Makino, Y. Hamada *Tetrahedron* **2008**, 64, 11568

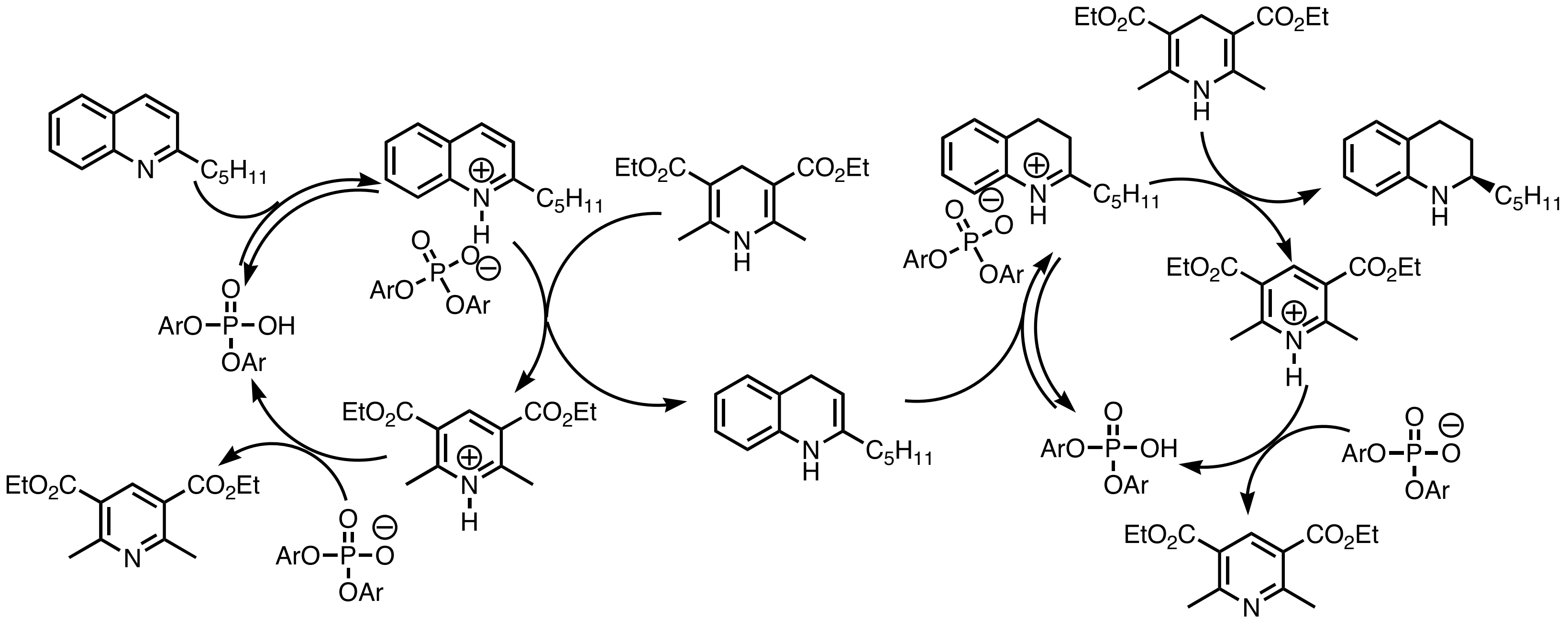
Coupled Imine/Enamine Organocascade



B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su, J.-H. Liao *JOC*, **2007**, 72, 8459

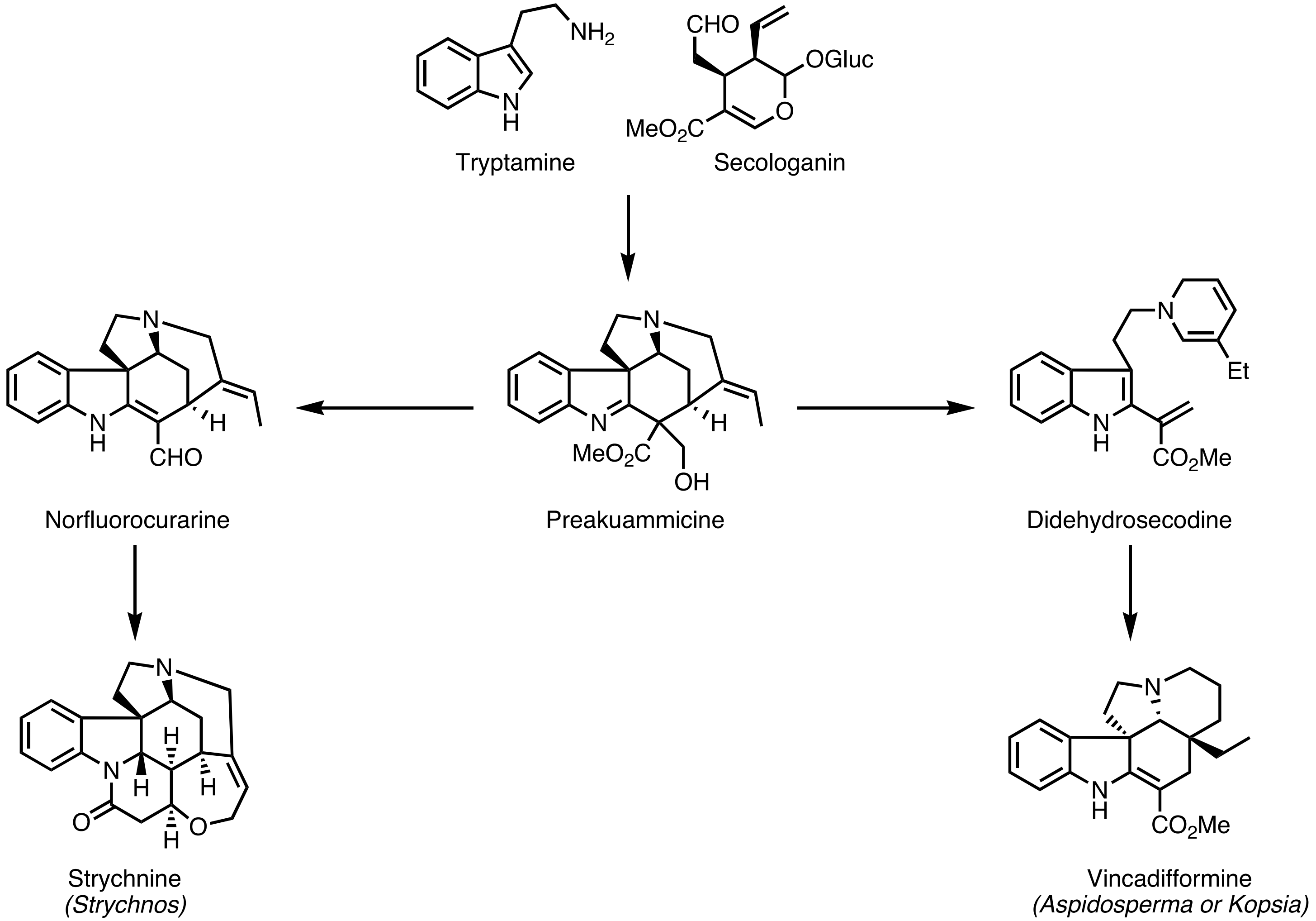
Bronsted-Acid Catalysed Cascade





M. Rueping; A.P. Antonchick; T. Theissmann, *ACIE*, **2006**, 45, 3683

Biosynthetic Intermediates to Title Paper Targets



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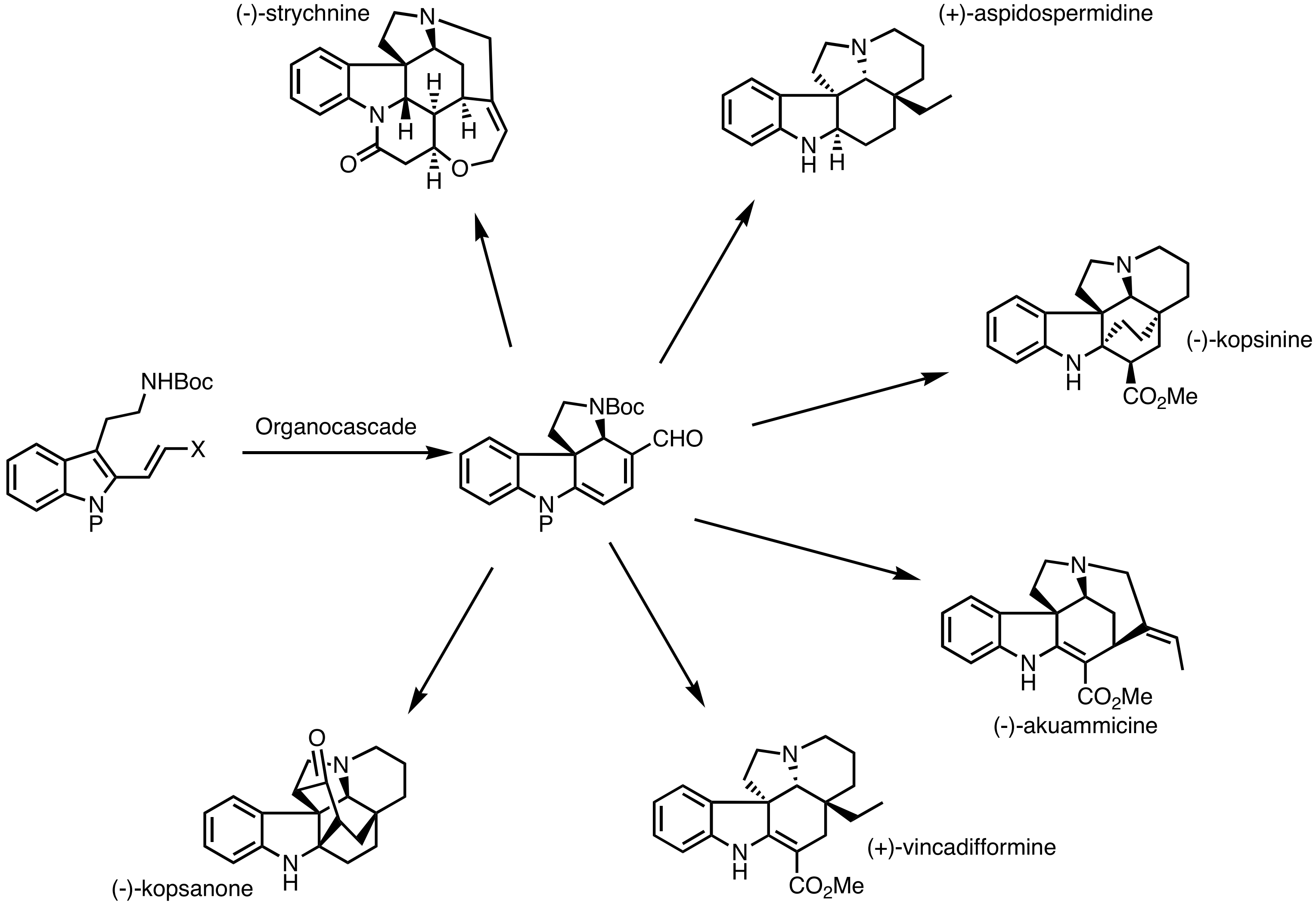
Natural Products Derived from a Common Intermediate



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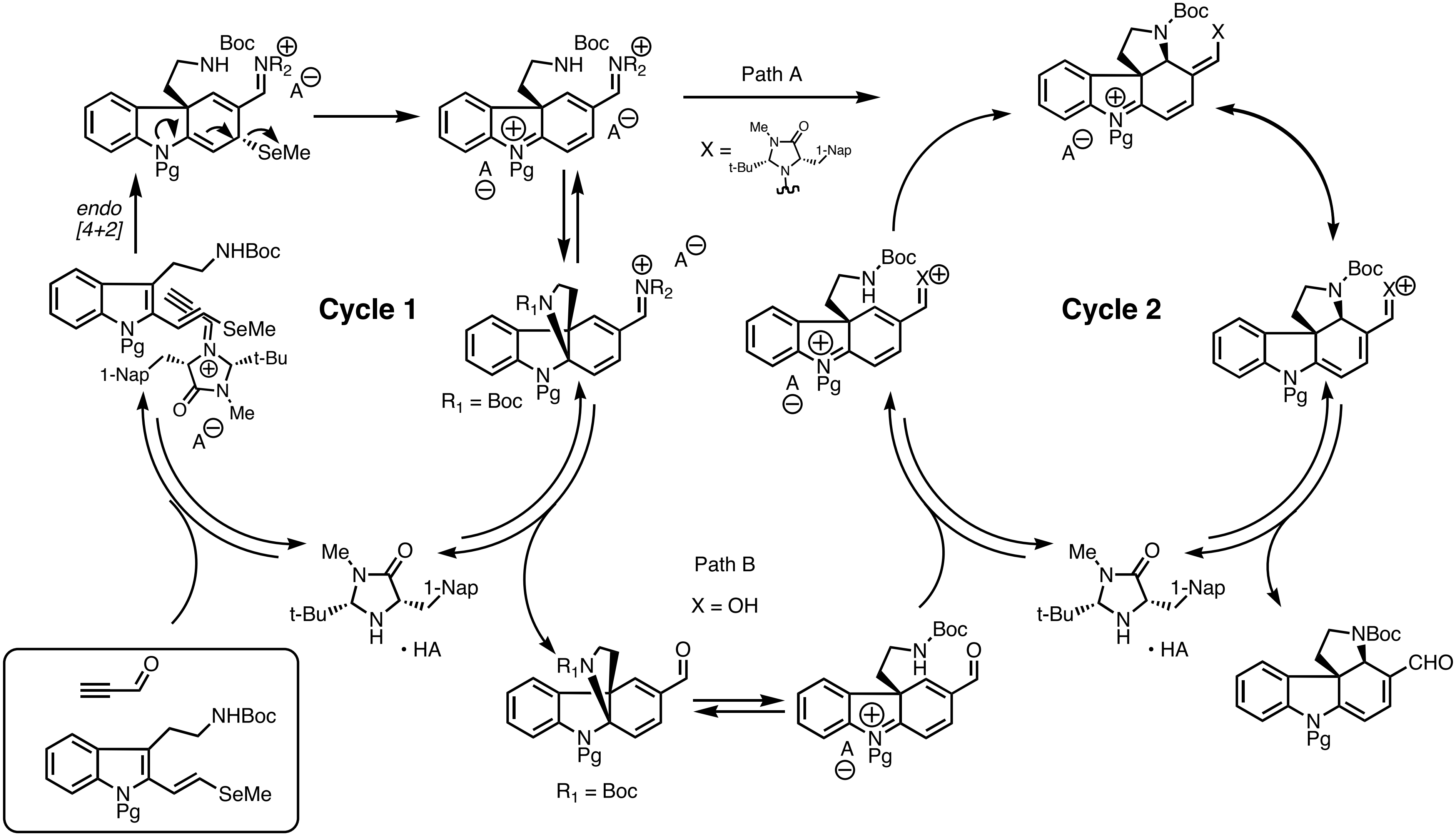
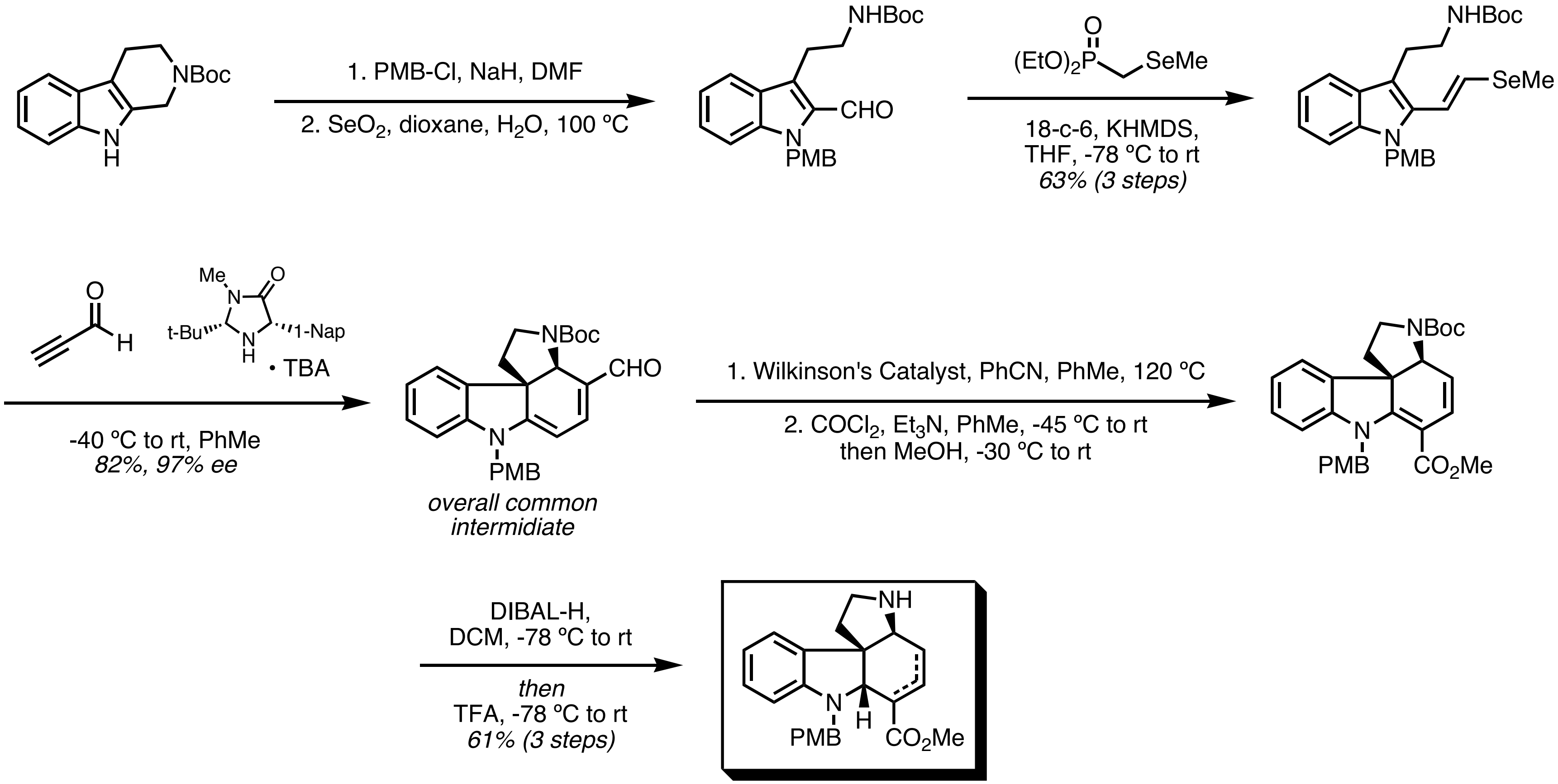
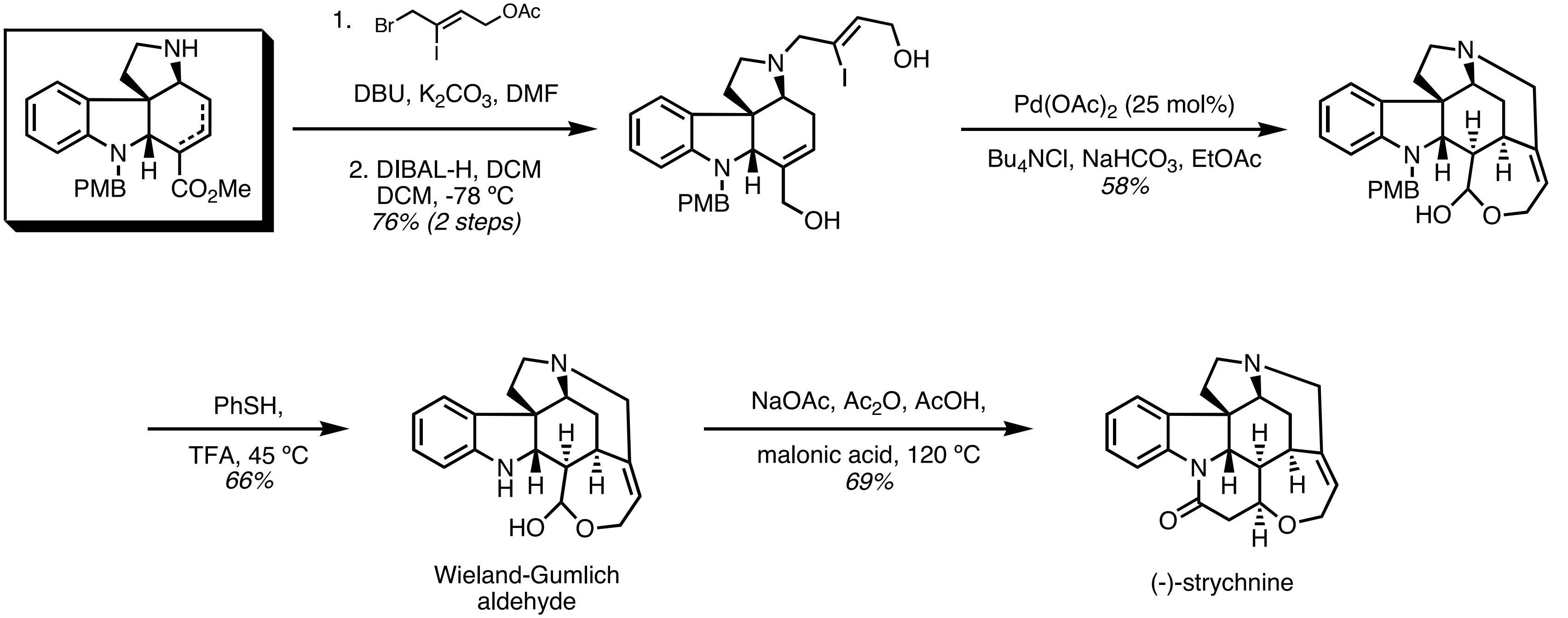
Mechanism of Organocascade cycles



Synthesis Towards Strychnine and Akuammicine



Completion of (-)-Strychnine

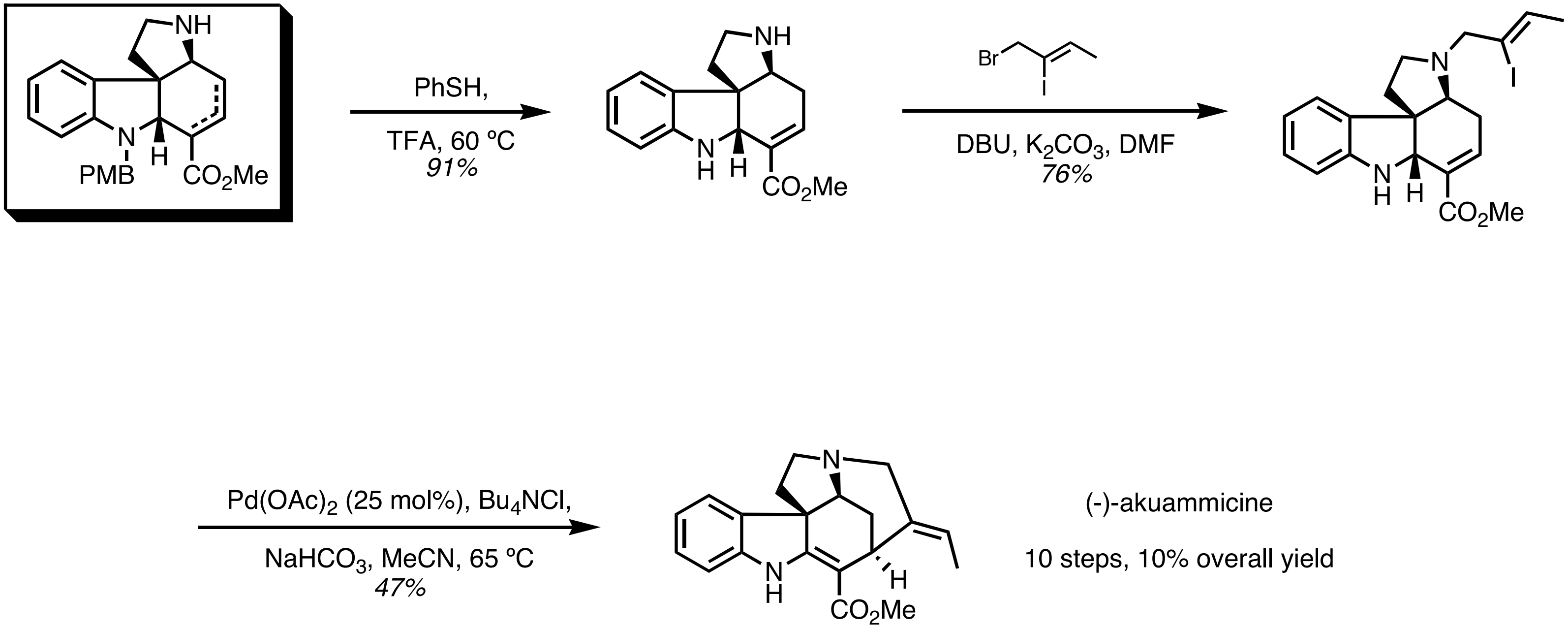


Wieland-Gumlich aldehyde

(-)-strychnine

12 steps, 6.4% overall yield

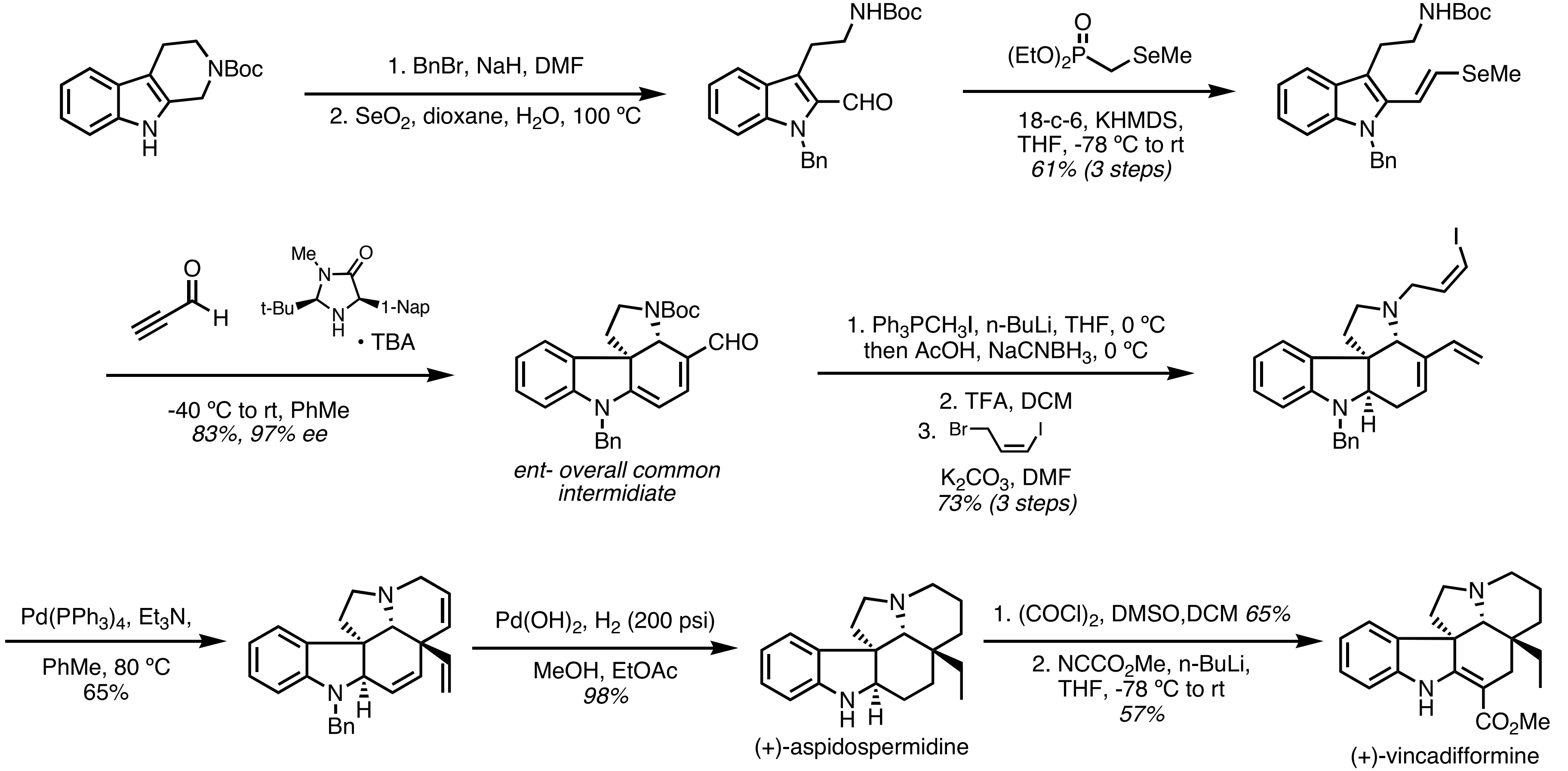
Completion of (-)-Akuammicine



(-)-akuammicine

10 steps, 10% overall yield

Synthesis of (+)-Aspidospermidine and (+)-Vincadifformine



ent- overall common intermidiate

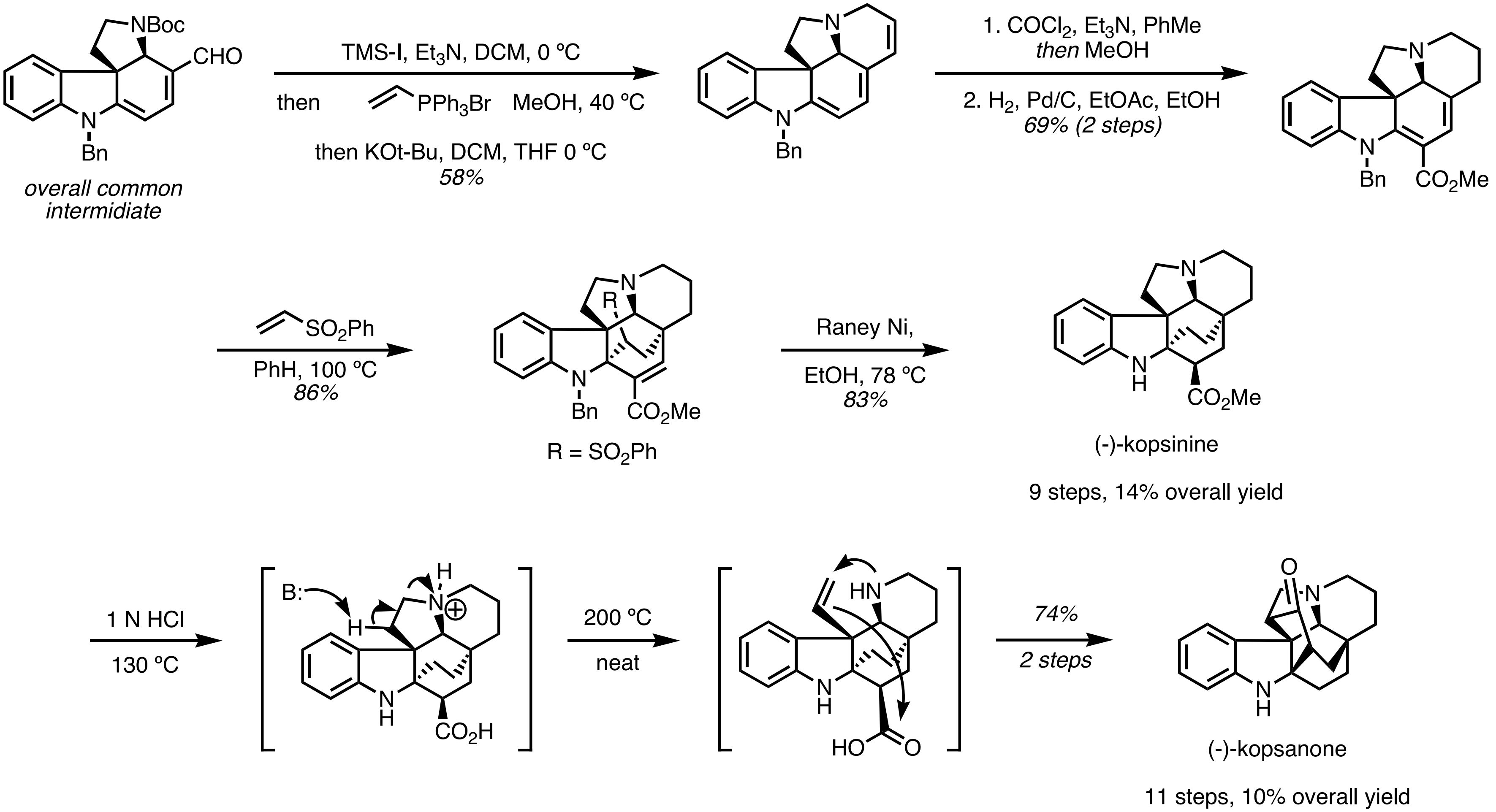
(+)-aspidospermidine

9 steps, 24% overall yield

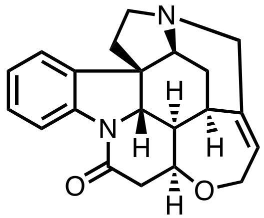
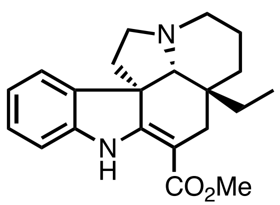
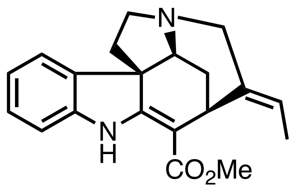
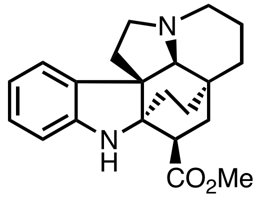
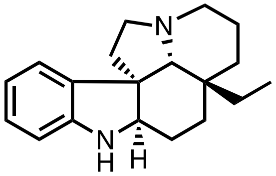
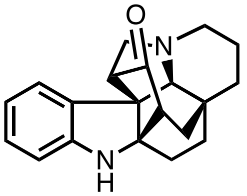
(+)-vincadifformine

11 steps, 8.9% overall yield

Synthesis of (-)-Kopsinine and (-)-Kopsanone



Title Paper Syntheses vs. Previous Syntheses

	Title Paper # steps (overall yield)	PSAC (overall yield)	PSCA (overall yield)		Title Paper # steps (overall yield)	PSAC (overall yield)	PSCA (overall yield)
 (-)-strychnine	12 (6.4)	25 (3)	16 (0.15)	 (+)-vincadifformine	11 (8.9)	NA	10 (8.5)
 (-)-akuammicine	10 (10)	NA	NA	 (-)-kopsinine	9 (14)	NA	19 (2.6)
 (+)-aspidospermidine	9 (24)	13 (NA^1)	11 (1.7)	 (-)-kopsanone	11 (10)	NA	NA

PSAC = Previous Shortest Asymetric Catalytic Synthesis
PSCA = Previous Shortest Chiral Auxiliary or Chiral Pool Synthesis

1 - unreported yields for some steps of the sequence

Summary

- An organo-catalyzed cascade was used to construct an advanced intermediate in the synthesis of a set of complex natural products.
- Six natural products were efficiently constructed enantioselectively from that advanced intermediate.
- All six syntheses represent some of the shortest routes to the respective targets.