

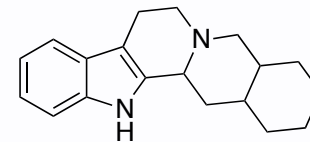
A Divergent Approach to The Synthesis of The Yohimbinoïd Alkaloids Venenatine and Alstovenine

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Tantillo, R. Sarpong

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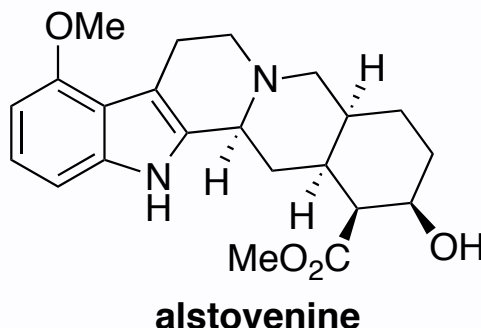
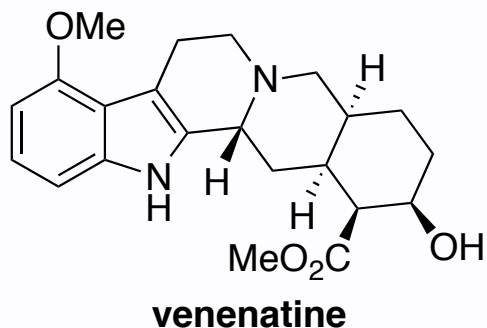
Corynanthe Alkaloids



Alstovenine/venenatine: isolated from the Bark of *Alstonia Venenata* (poison devil tree) along with various others alkaloids (reserpine, yohimbine...). Traditionally used in ayurvedic medicine.



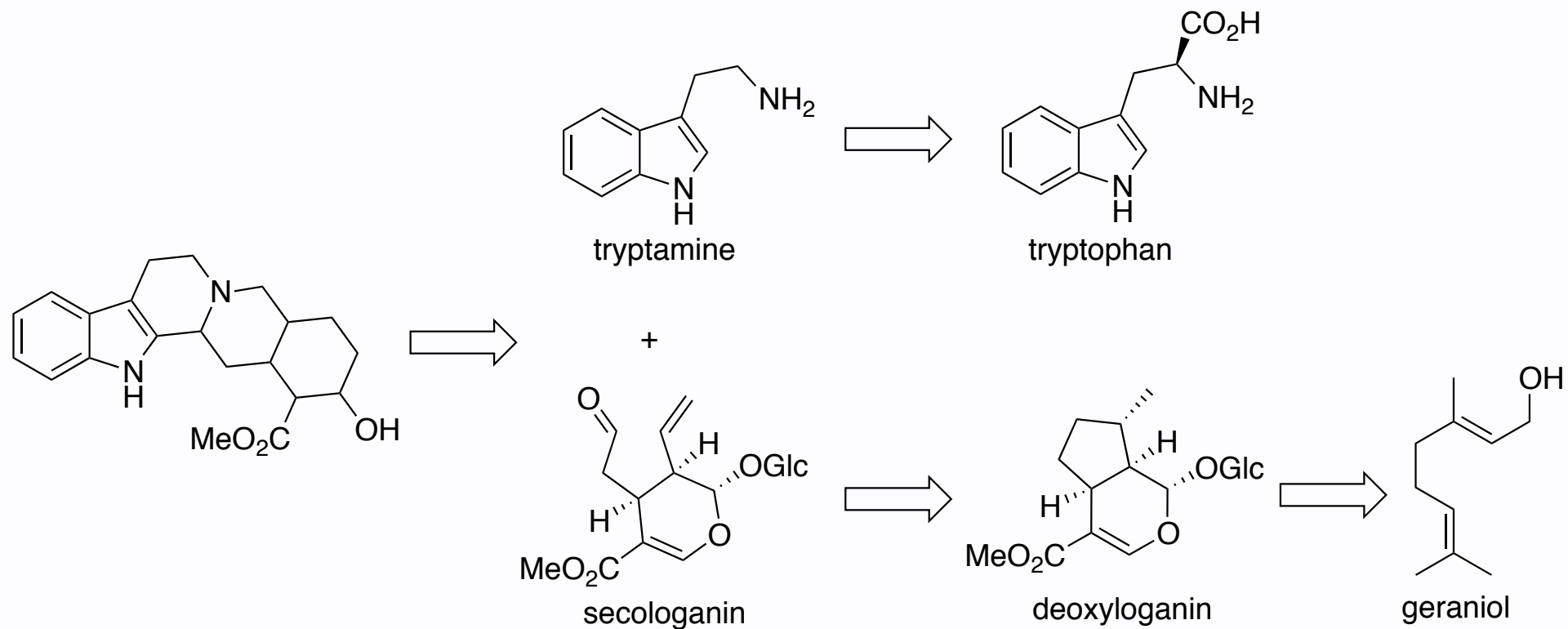
Alstonia venenata



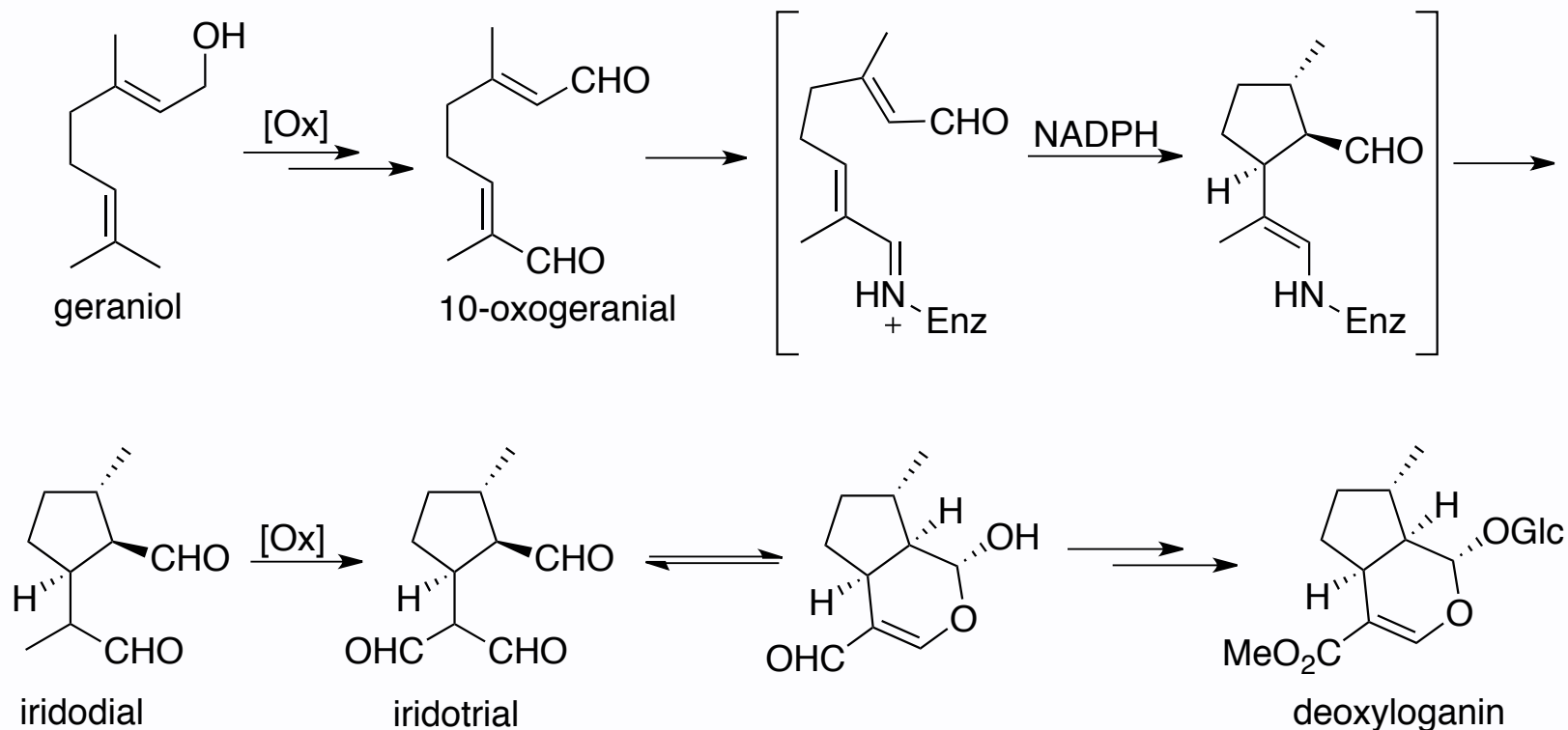
Terpenoid indoles alkaloids

Corynanthe type alkaloids found in many other plant species (e.g. reserpine in *Rauwolfia serpentina*)

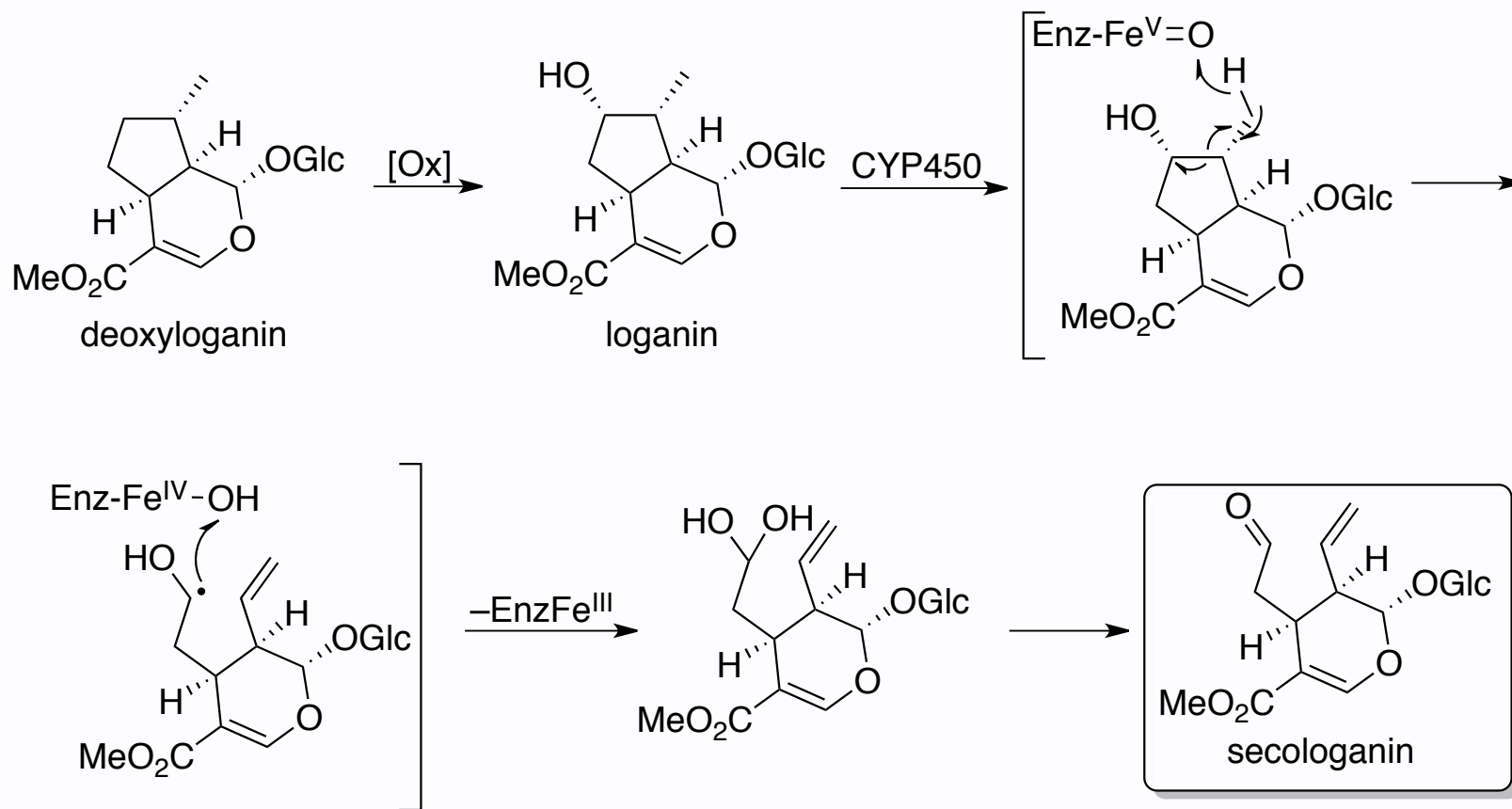
General Biosynthetic Pathway



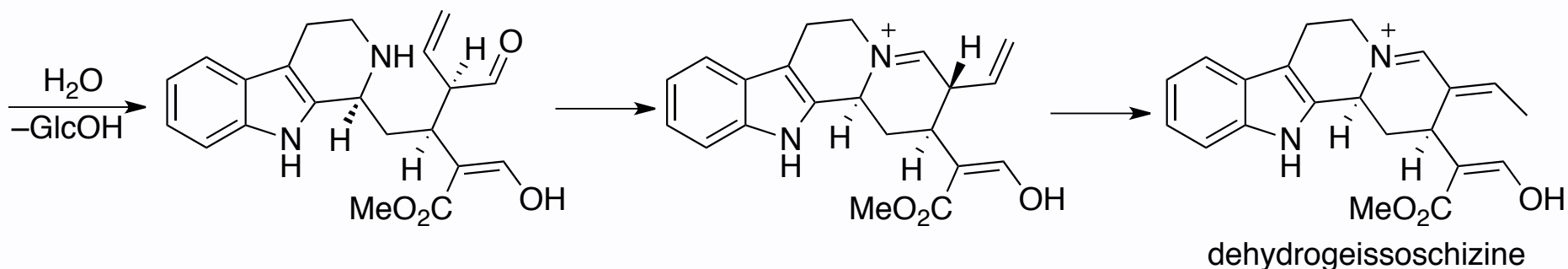
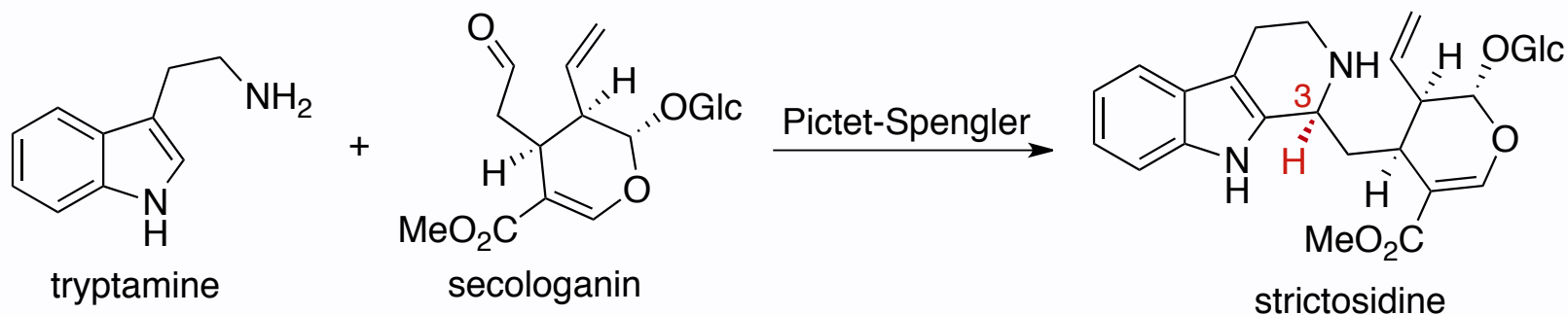
Deoxyloganin Biosynthesis



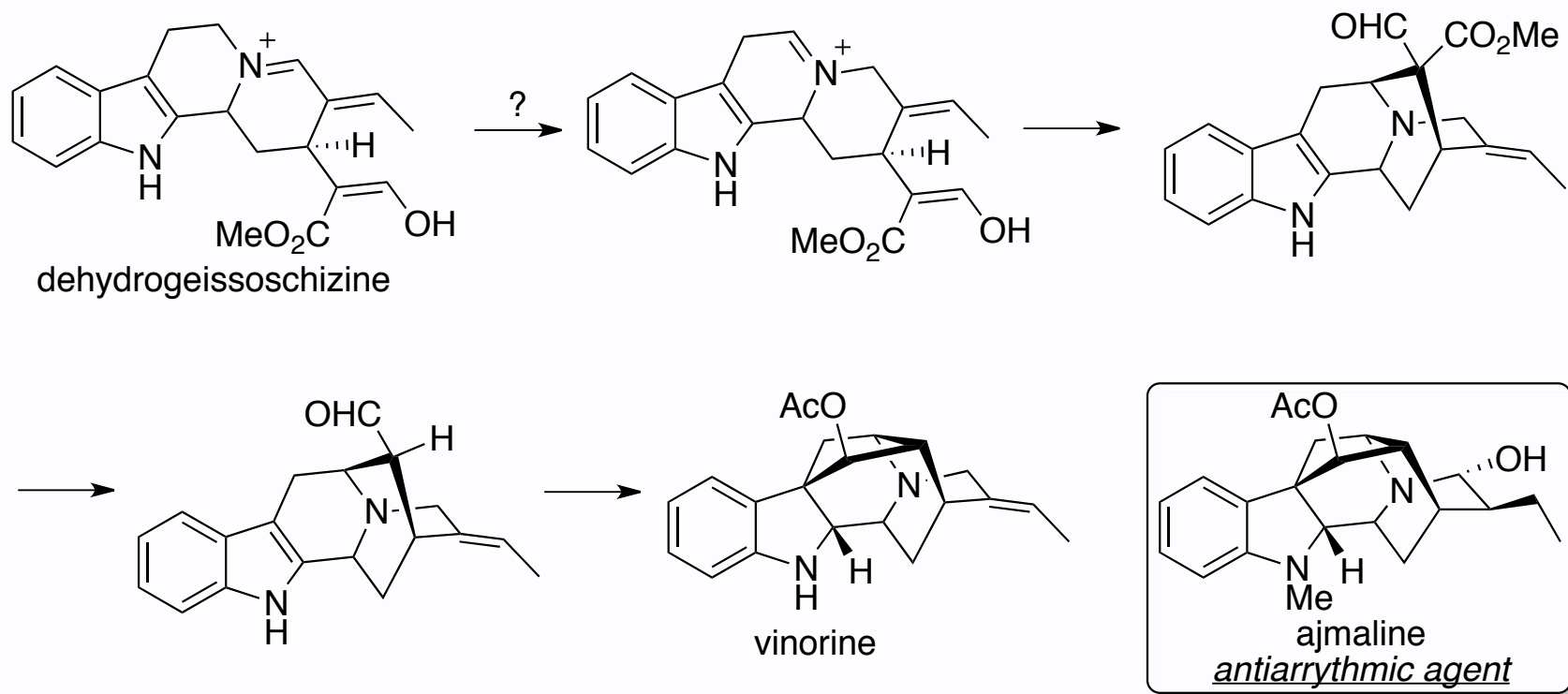
Secologanin Biosynthesis



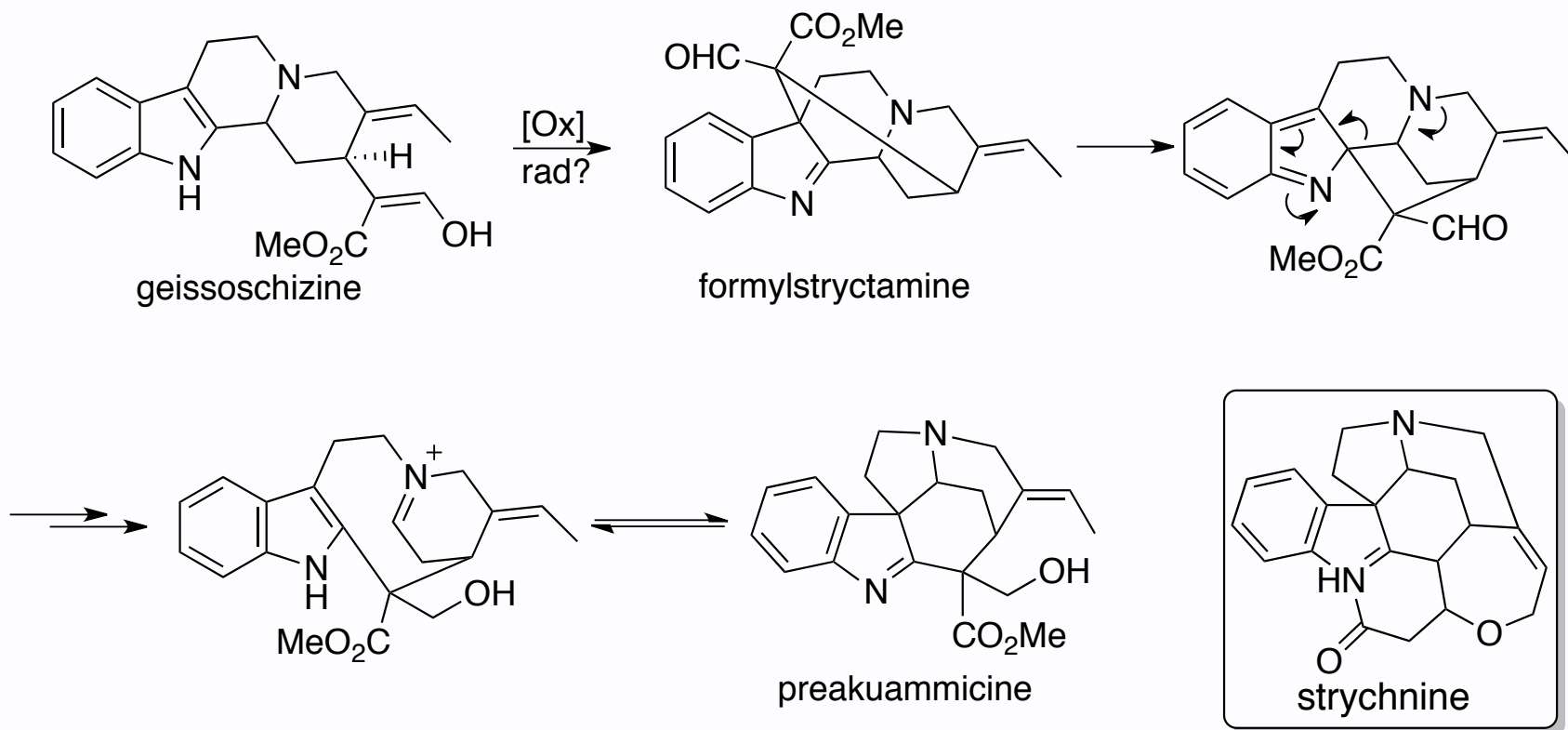
Geissoschizine Biosynthesis



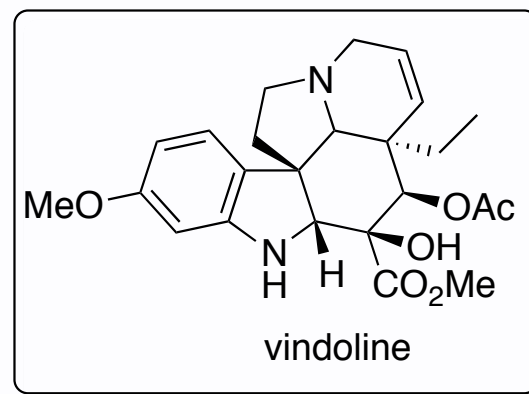
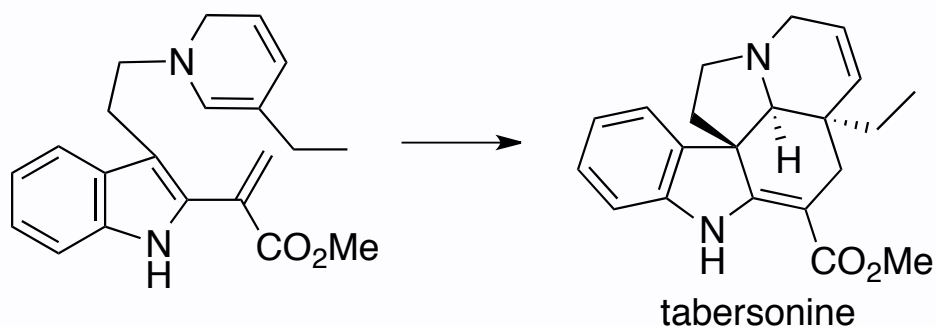
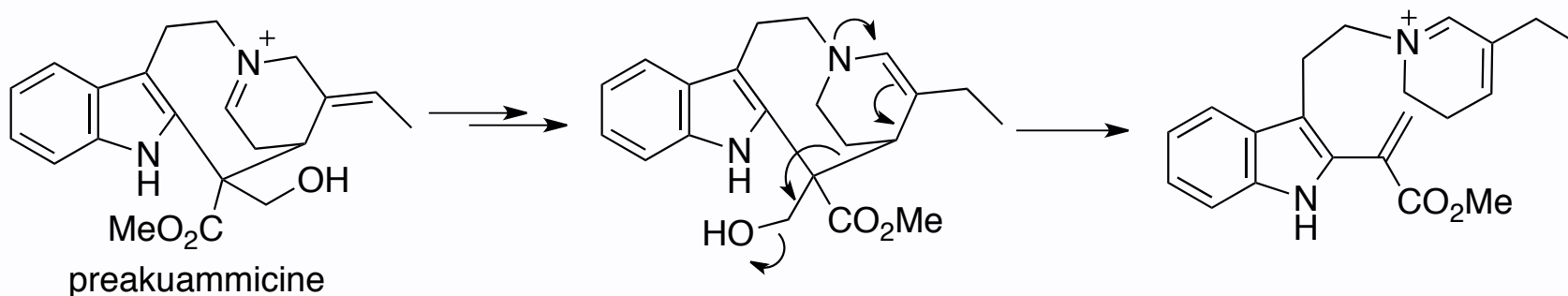
Related Alkaloids: Ajmaline



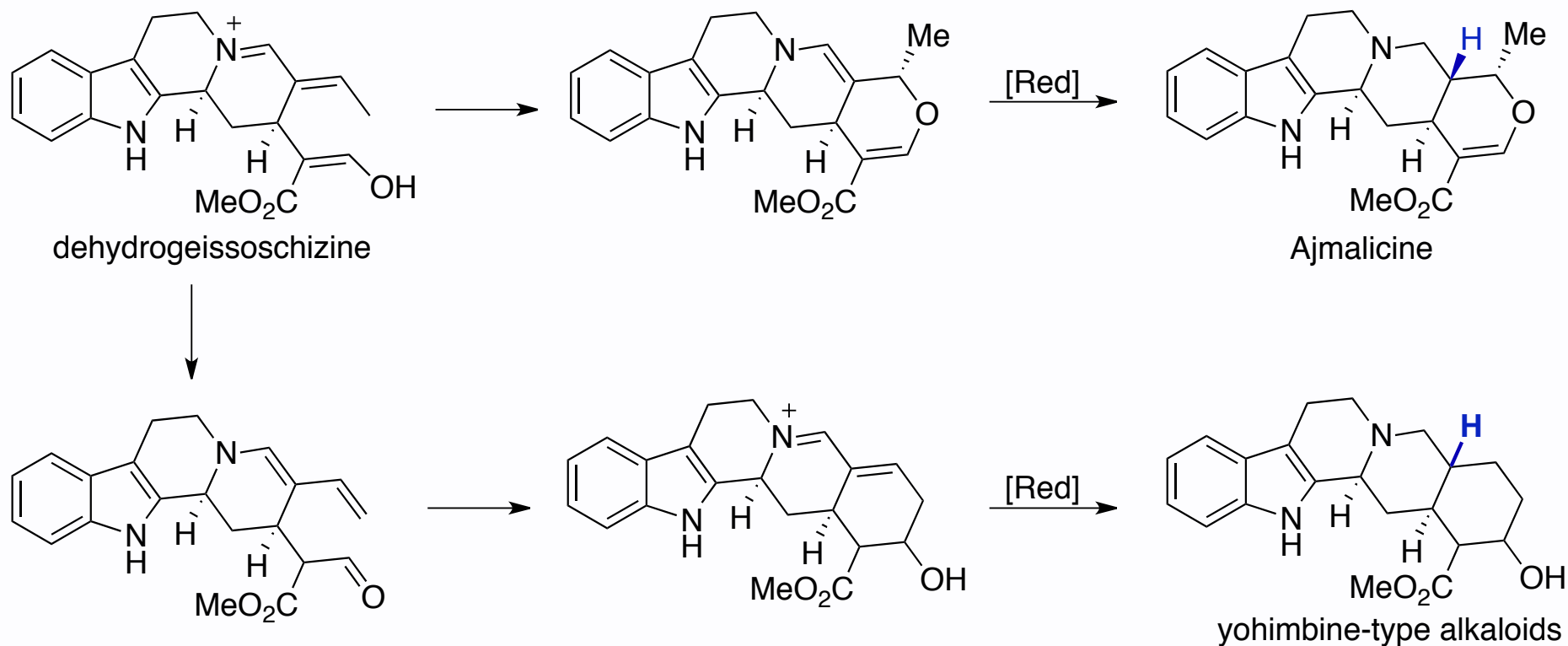
Related Alkaloids: *Strychnos*



Related Alkaloids: *Aspidosperma*



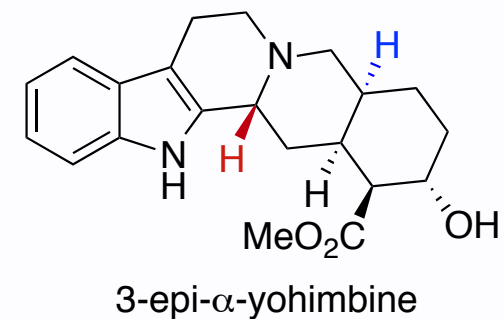
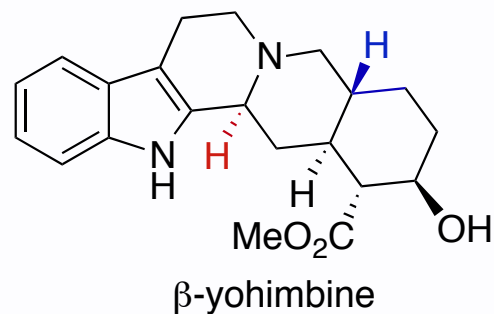
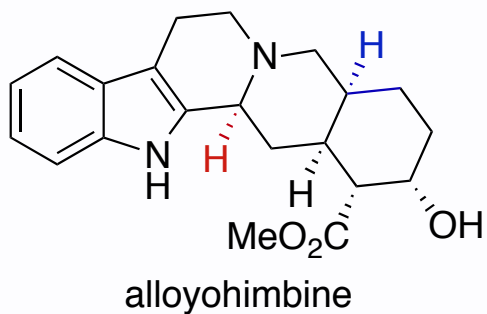
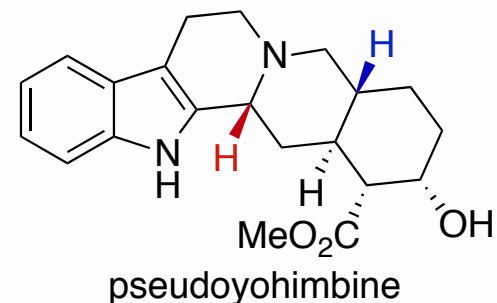
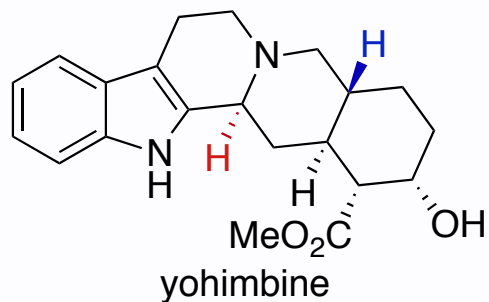
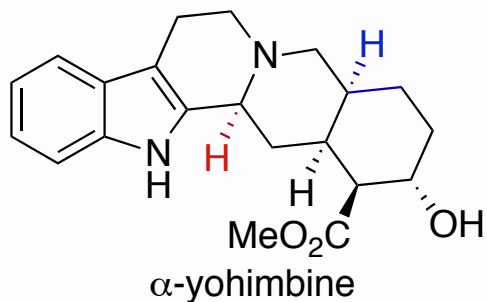
Corynanthe Alkaloids Biosynthesis



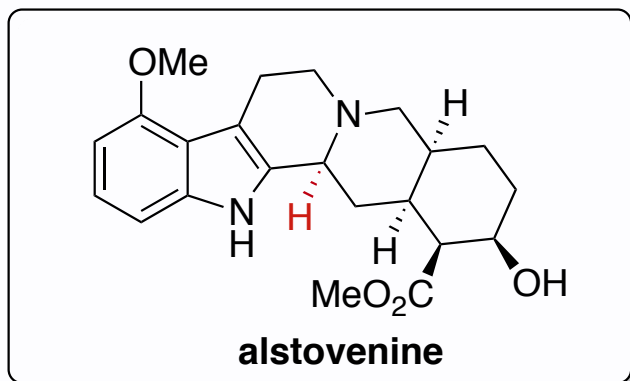
S. E. O'Connor, J. J. Maresh, *Nat. prod. Rep.* **2006**, *23*, 532–547.

P. M. Dewick, *Medicinal Natural products*, John Wiley & Sons, Chichester, 2002, p.351–352. ⁹

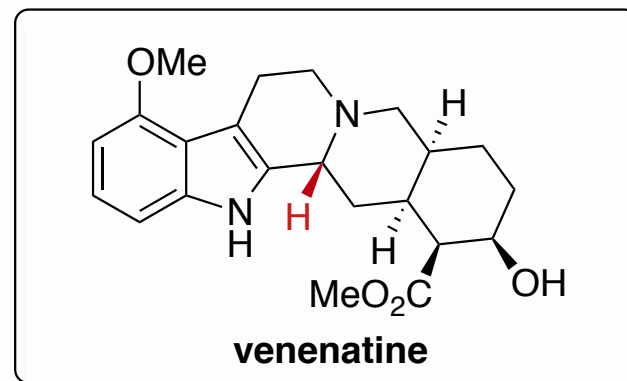
Yohimbine Type Alkaloids



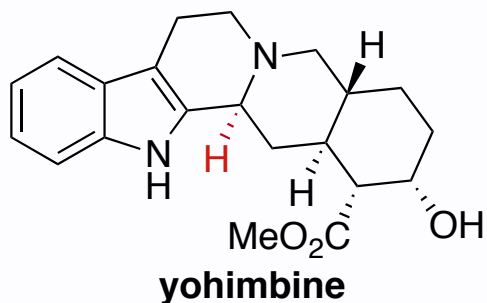
Pharmacological Activities



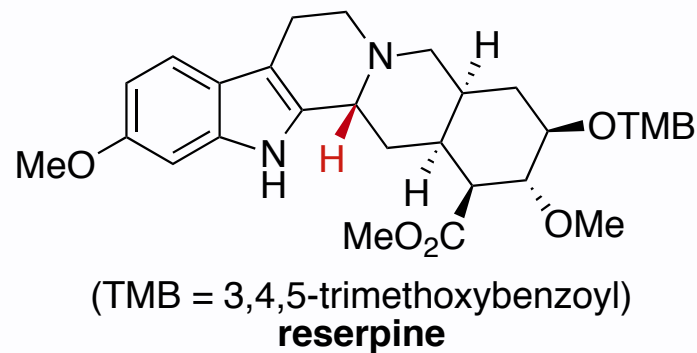
CNS stimulant (1 mg kg⁻¹/mice)
Monoamine Oxidase Inhibitor (MAOI)



CNS depressant



Stimulant and aphrodisiac
Treatment of male impotence

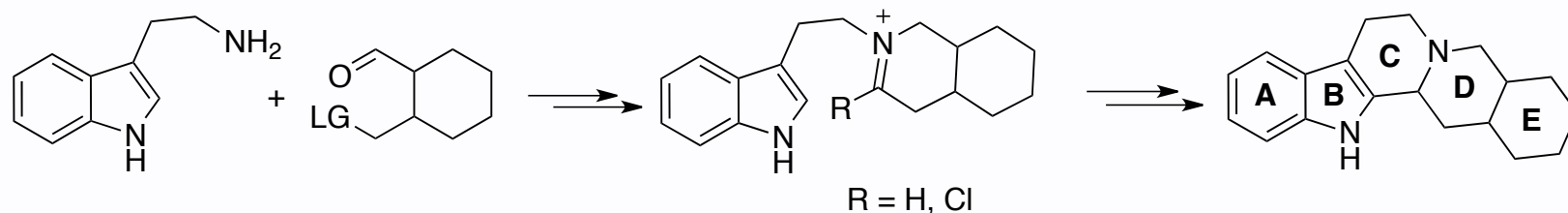


CNS depressant
tranquilliser, antihypertensive

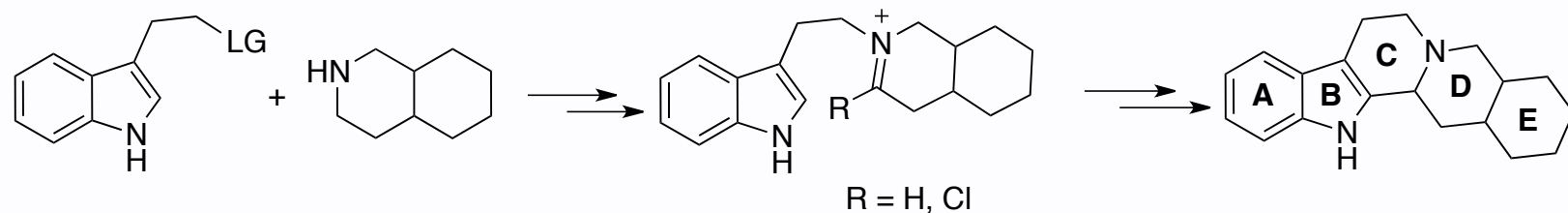
General Synthetic Strategy

Various approaches for the synthesis of corynanthe alkaloids

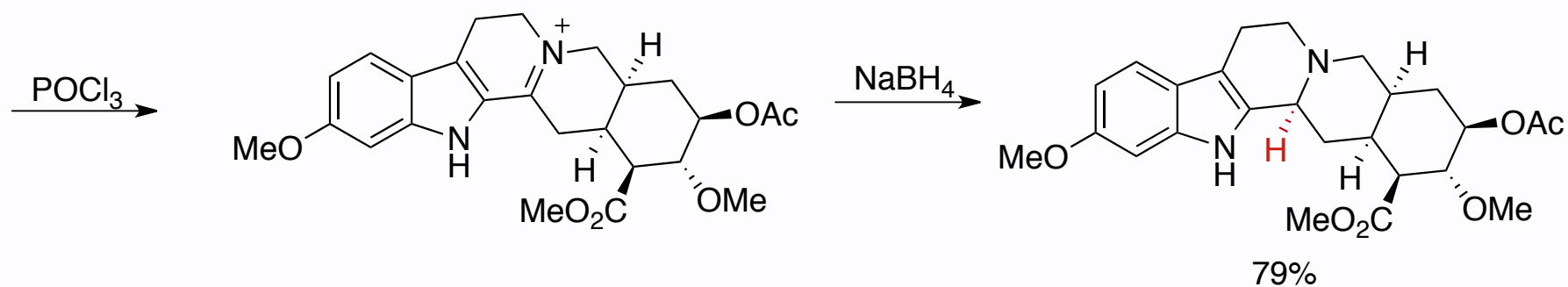
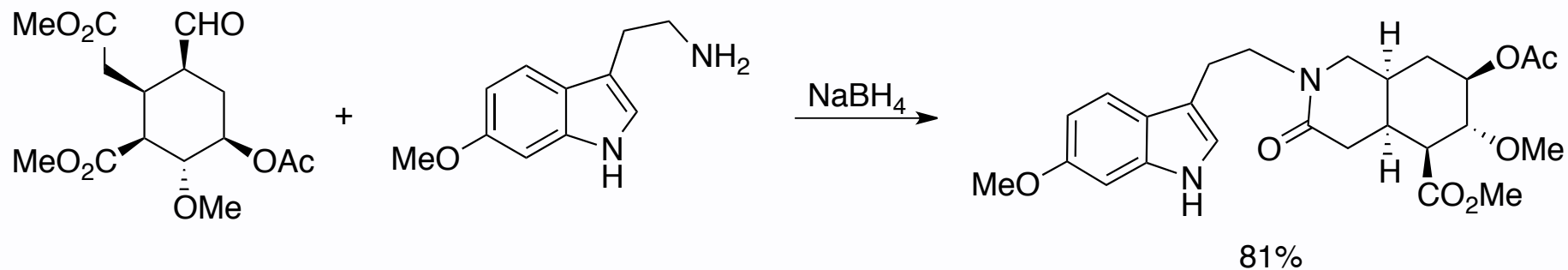
Most of them relied on the preparation of the E-ring, followed by condensation with a tryptamine derivative then Pictet-Spengler reaction.)



Some used a fused DE ring coupled with an ethylindole derivative finished then nucleophilic attack of the indole on a suitable iminium electrophile

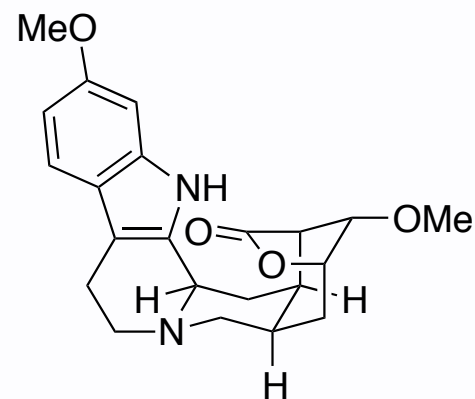
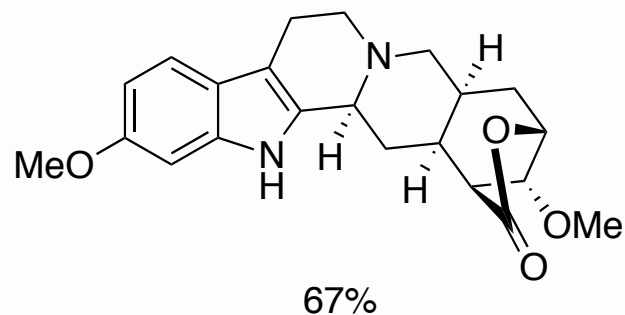


Woodward's Synthesis

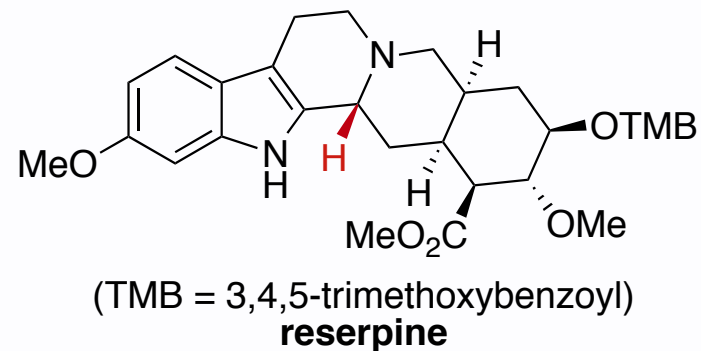
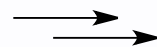
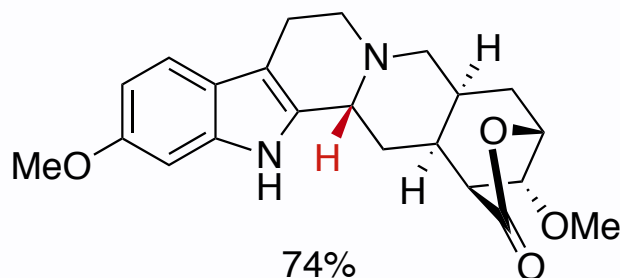


Woodward's Synthesis

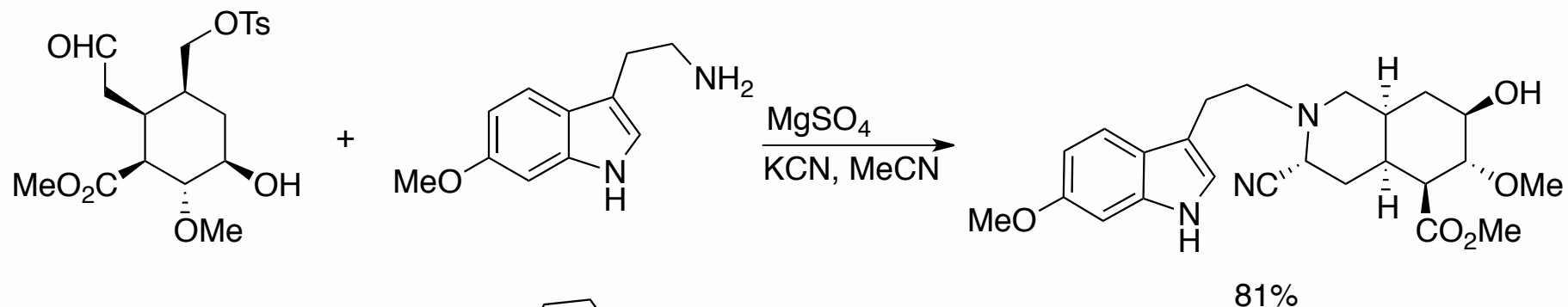
1) KOH, MeOH
2) DCC, pyridine



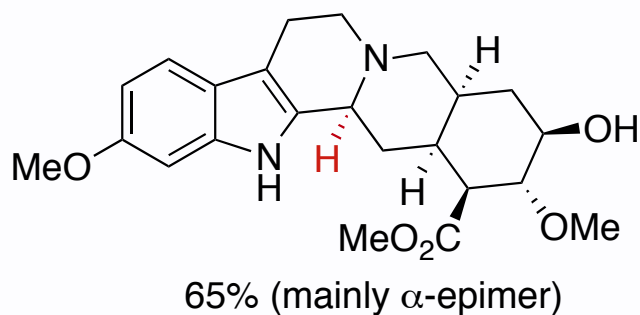
t-BuCO₂H
reflux



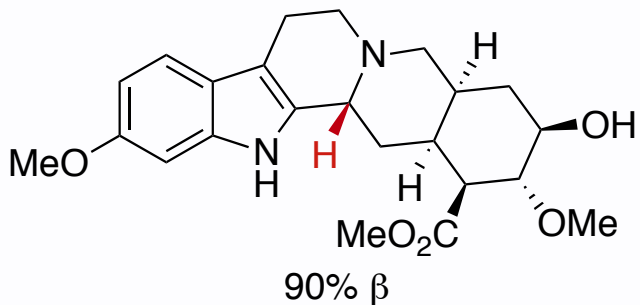
Stork Synthesis



$\xrightarrow[\text{reflux}]{\text{MeCN}}$

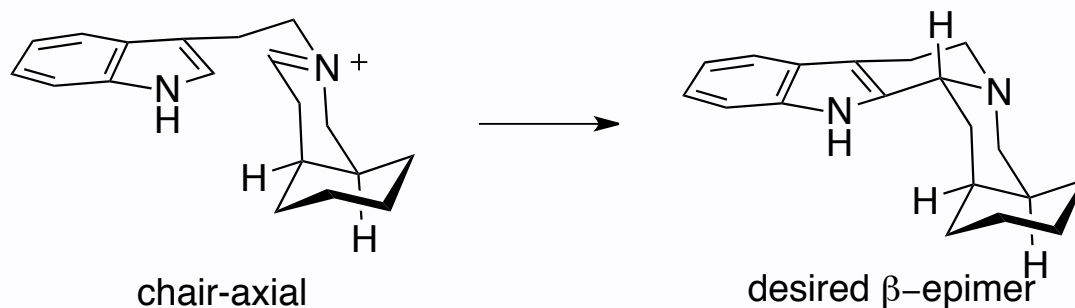


$\xrightarrow[\text{THF, rt}]{\text{HCl}}$

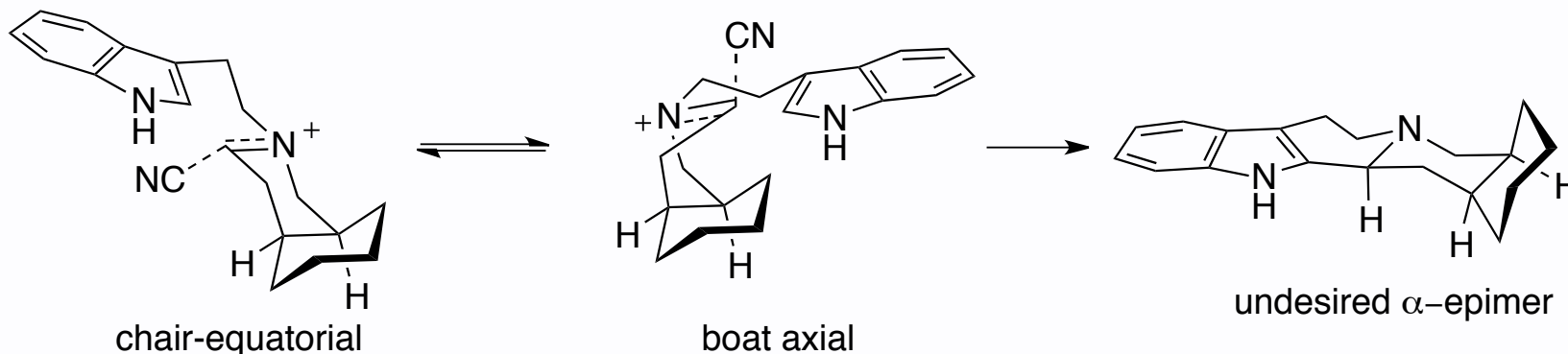


Tight Ion Pair?

Free iminium ion (THF, HCl). Kinetically favored axial attack

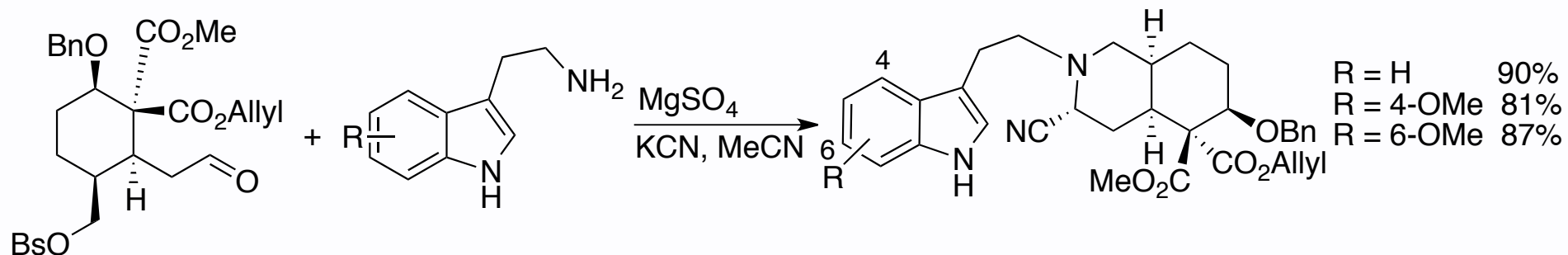
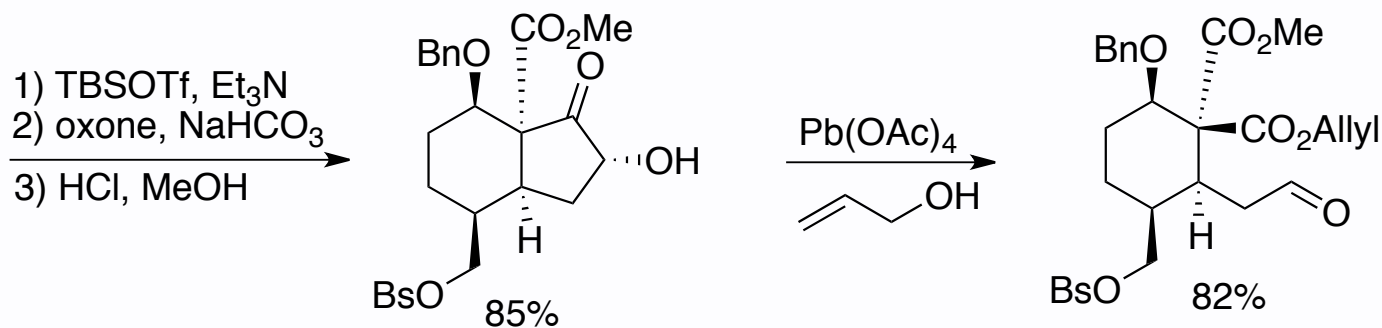
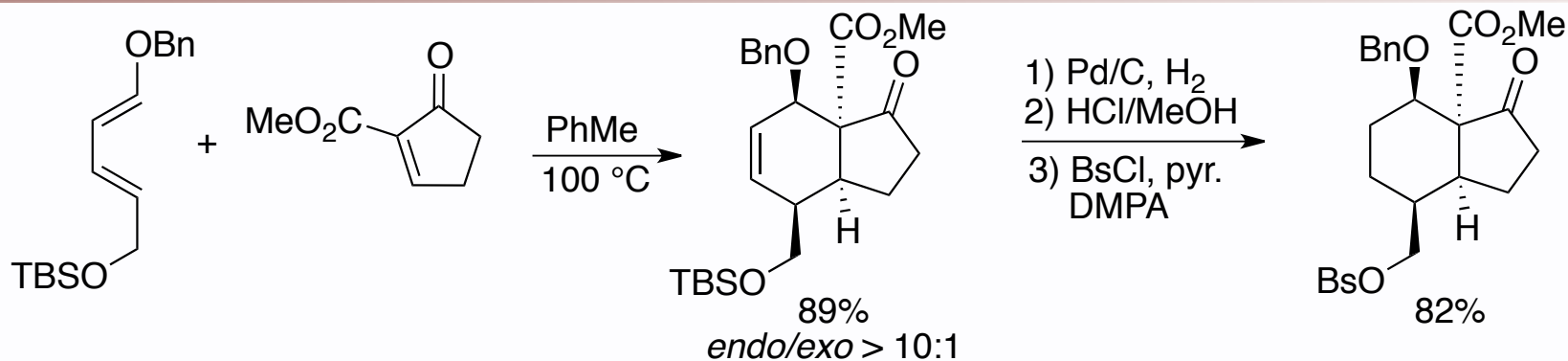


Tight ion pair (MeCN, reflux). Chair-axial blocked \rightarrow boat-axial

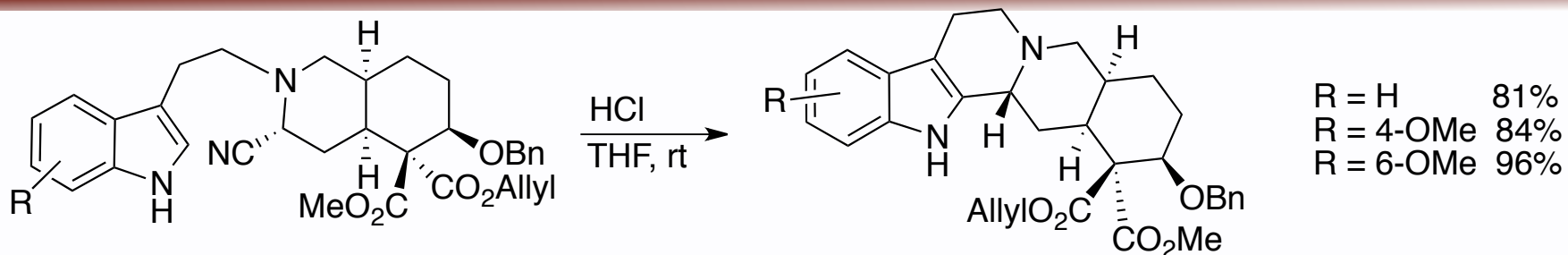


\rightarrow Sarpong: can this concept be extended to other Yohimbine alkaloids?

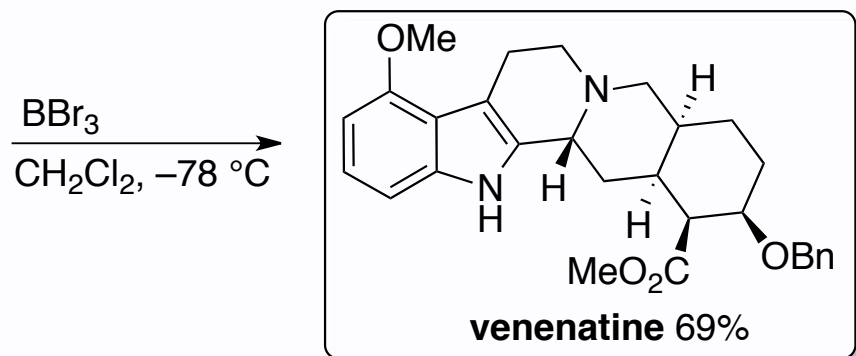
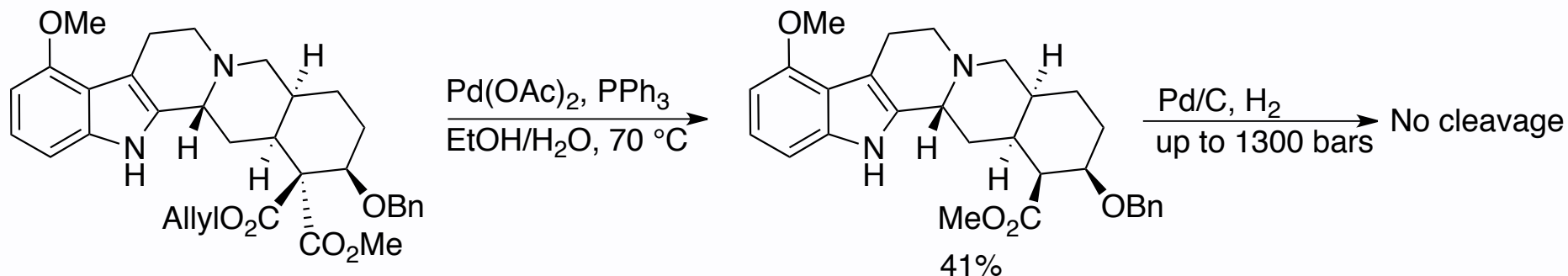
Sarpong Synthesis



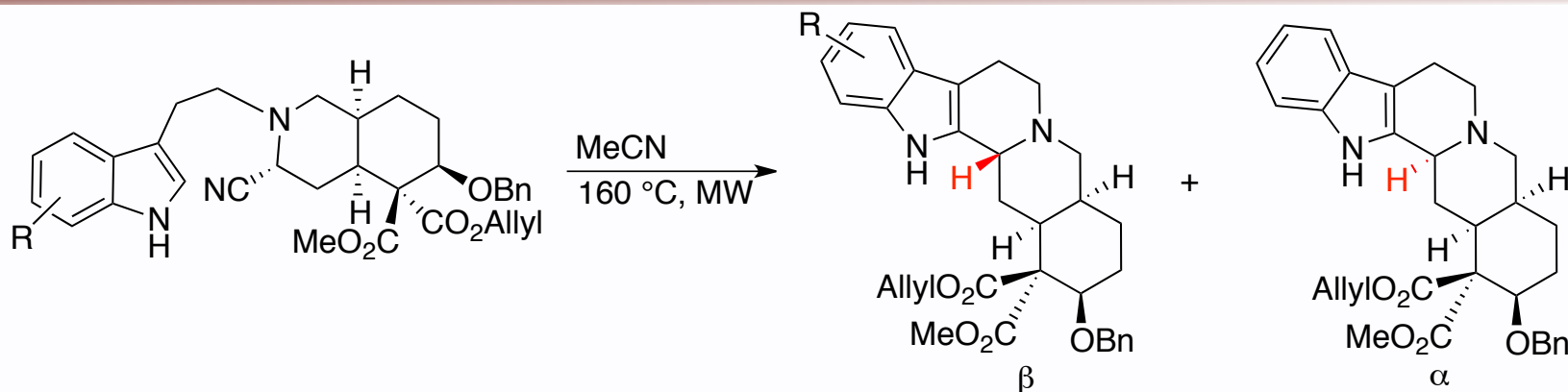
Kinetic Cyclisation: Venenatine



only β-epimer observed

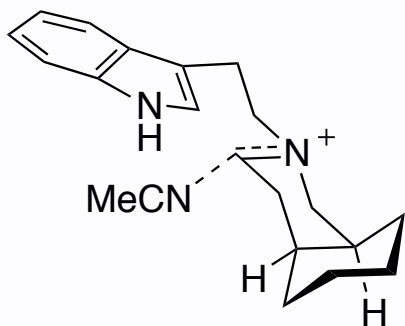


Thermal Cyclisation



R = H	53%	$\beta/\alpha = 1:3$
R = 4-OMe	72%	$\beta/\alpha = 1:1.8$
R = 6-OMe	96%	$\beta/\alpha = 1:8$

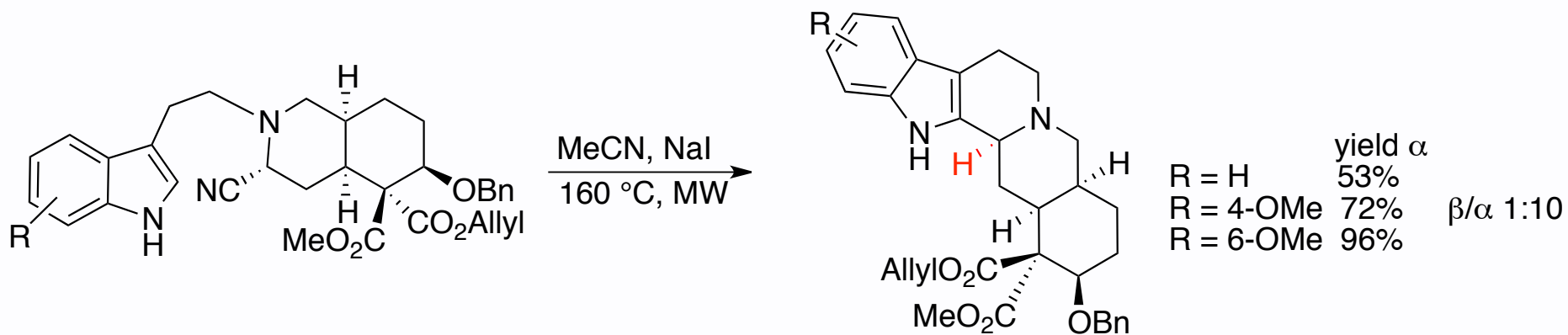
Best Nucleophile (6-Methoxyindole) gives the highest selectivity



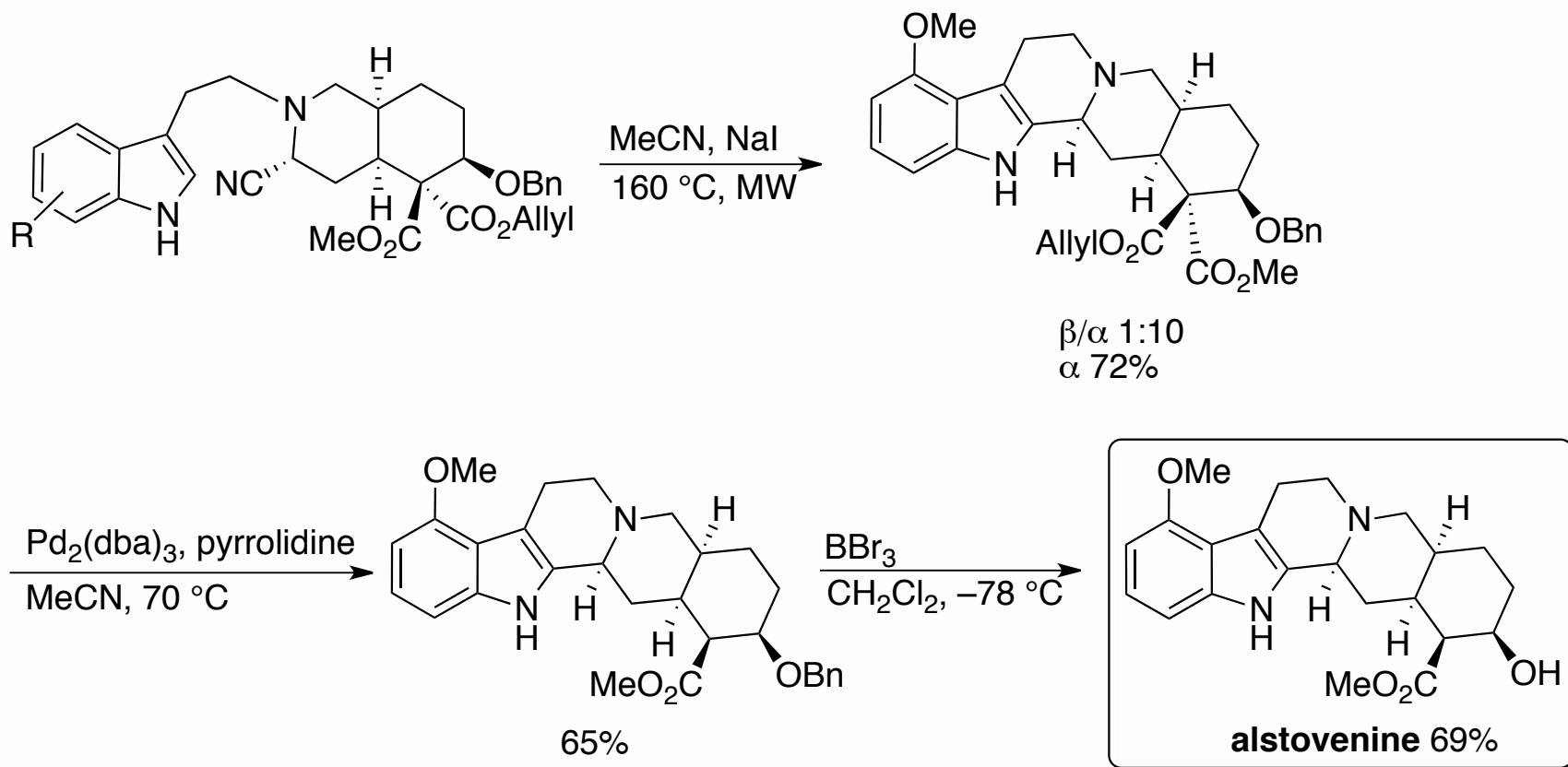
Direct S_N2 ? On the nitrile or on a solvent molecule?
 → Various solvents: poor selectivity, difficult to rationalize.

Nucleophile additives (DMAP, imidazole, NaI)
 → Improved selectivity for the α -epimer

Nal as an Additive



Alstovenine



Conclusions

Very much inspired by Stork!

Interesting result with a difficult substrate using NaI

What's the role of the nucleophile?

→ tight ion pair

→ S_N2-like reaction

More details would be appreciable (wait for the full paper)