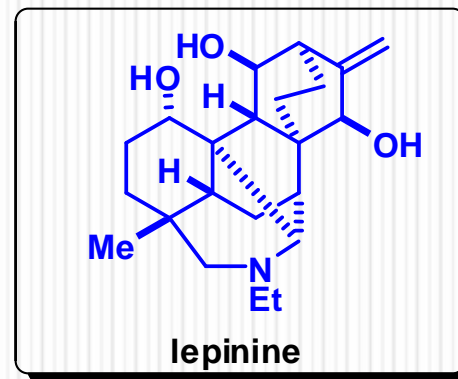


Total Synthesis of (-)-Lepinine

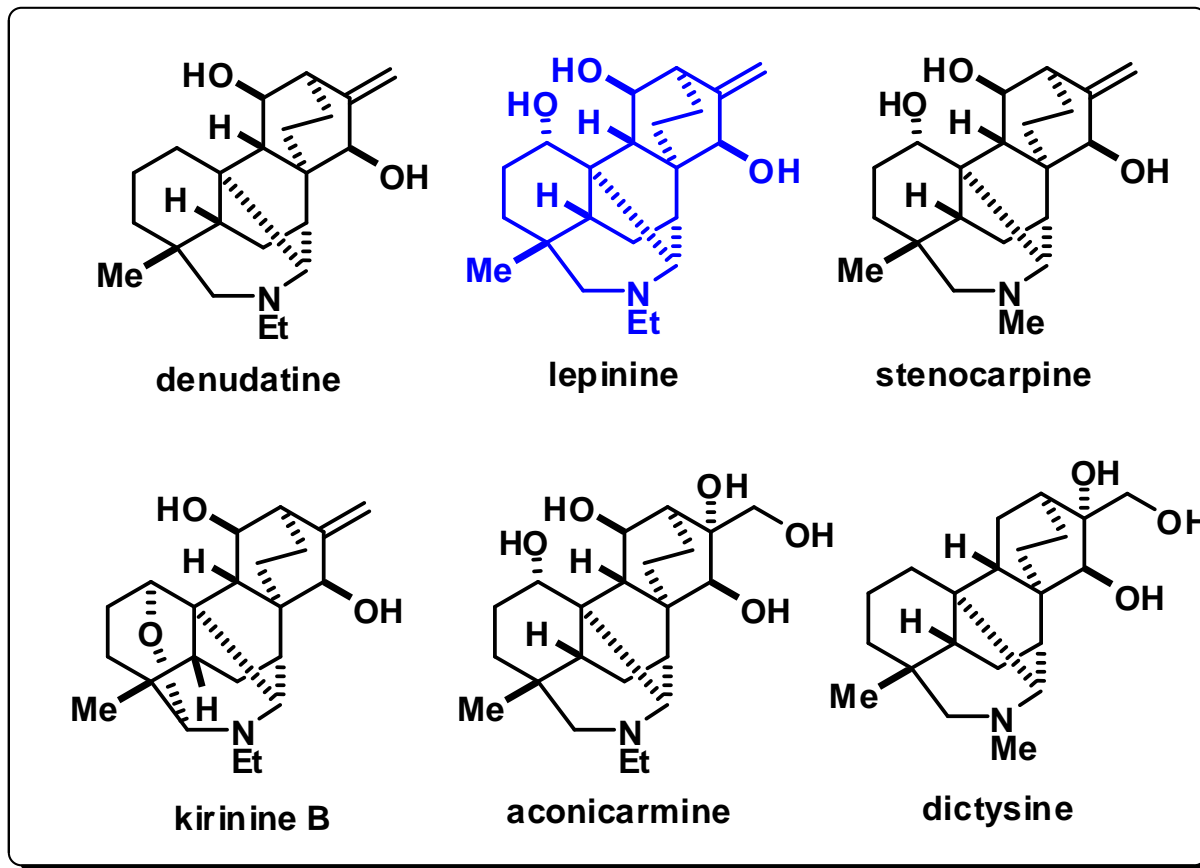
Sankar Rao Suravarapu

Prof. Dr. Philippe Renaud
University of Bern, Department of Chemistry
and Biochemistry



Introduction

1. Lepenine is a diterpene alkaloid which belongs to denudatine family
2. Contains challenging and very complex hexacyclic molecular architecture

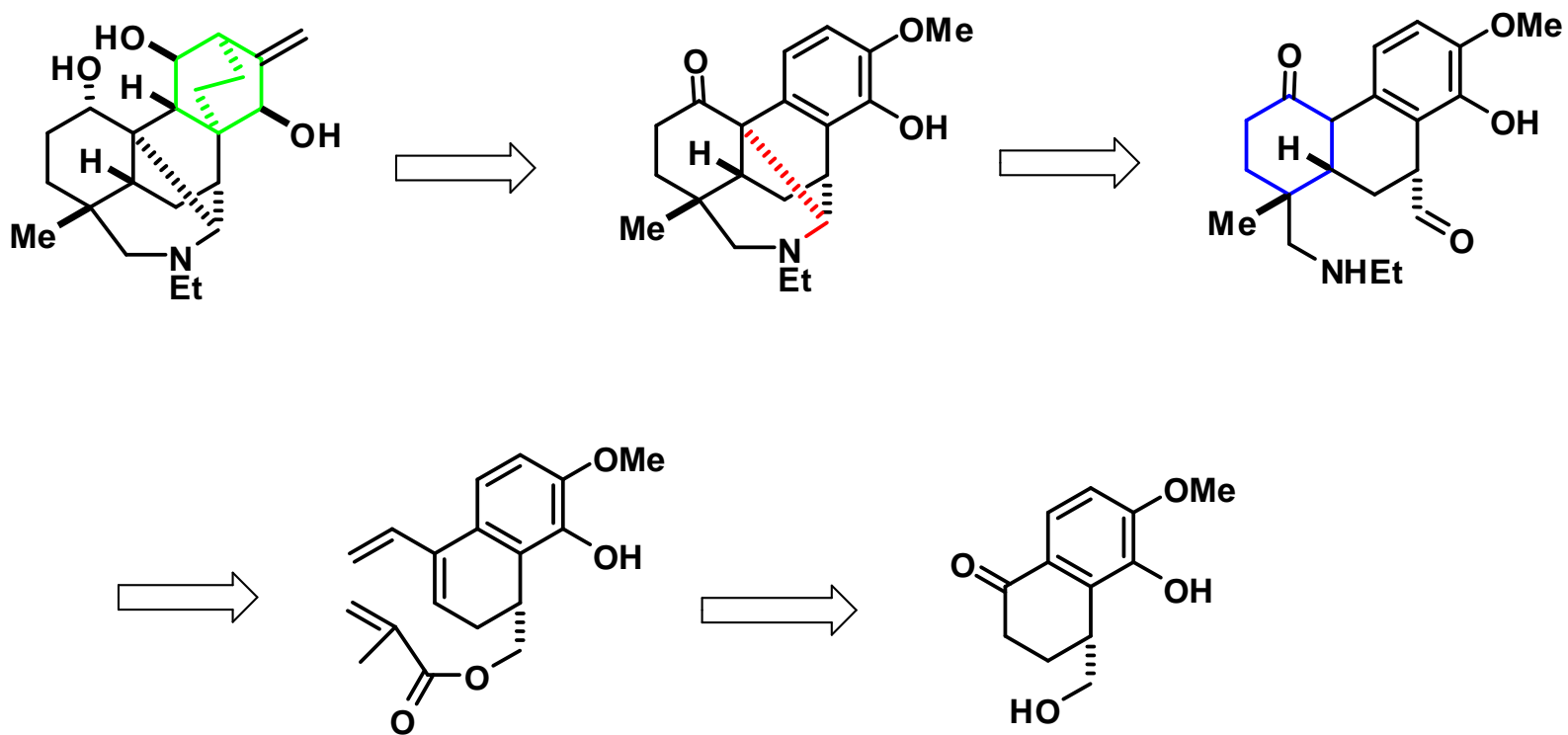


denudatine-type alkaloids

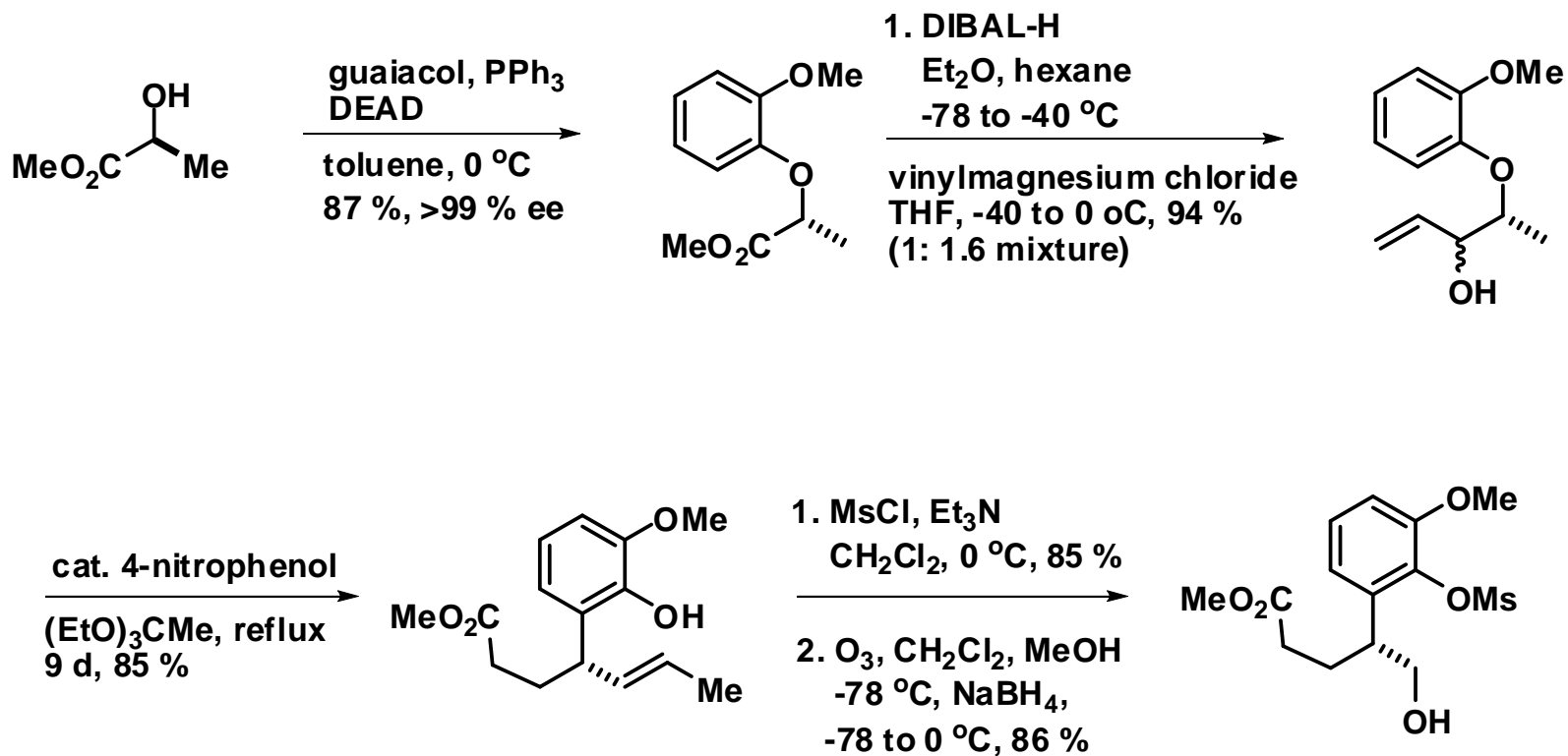
Introduction

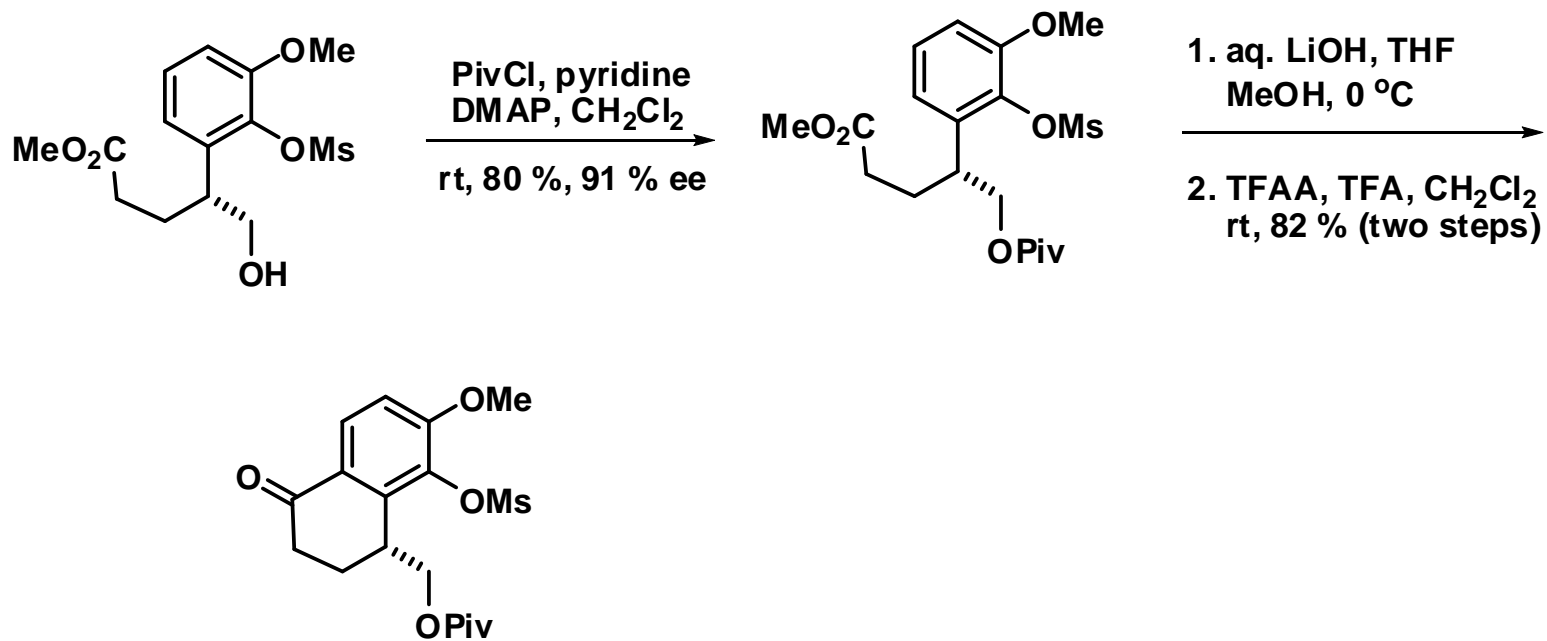
3. Interesting because they are chemical and biosynthetic precursors of aconitine-type alkaloids
4. These aconitine type alkaloids are well-known for their potent bioactivity such as inhibition of the voltage-dependent sodium ion channel

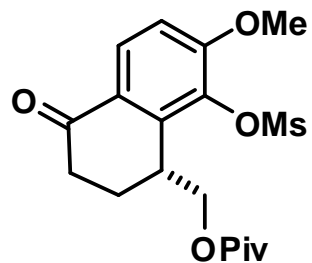
Retrosynthetic analysis



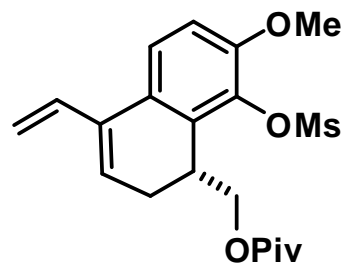
Synthesis of tetralone core



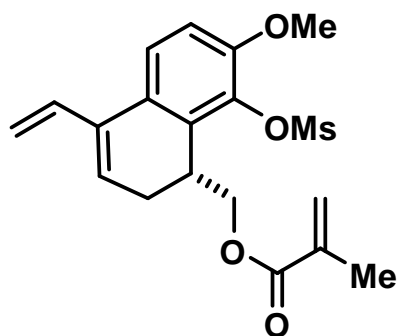




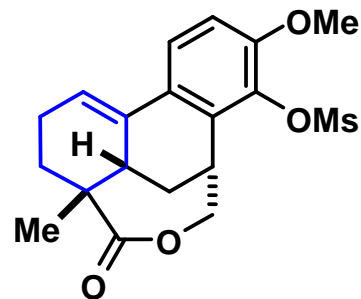
1. vinylmagnesium chloride
THF, -40 °C, 85 %
2. AgOTf (5 mol%)
toluene, reflux
1 h, 63 %



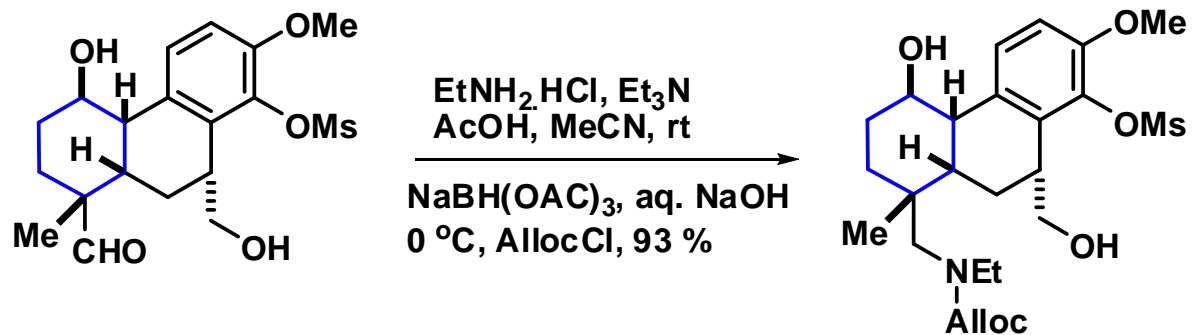
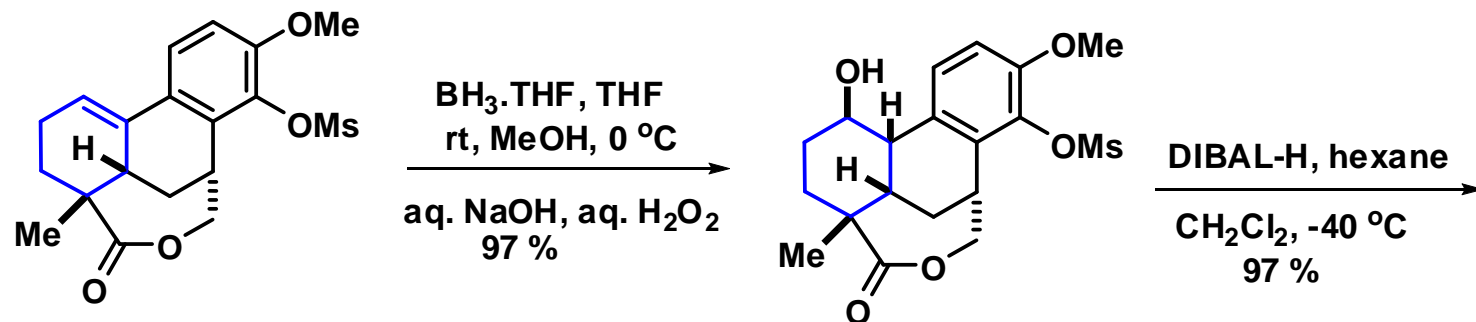
1. DIBAL-H, hexane
CH₂Cl₂, 0 °C, 89 %
2. methacrylic acid, DCC
DMAP, CH₂Cl₂,
rt, 85 %

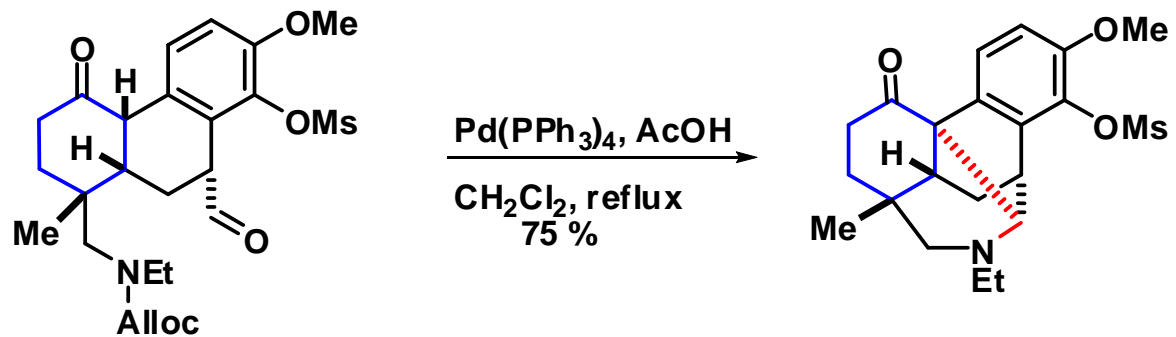
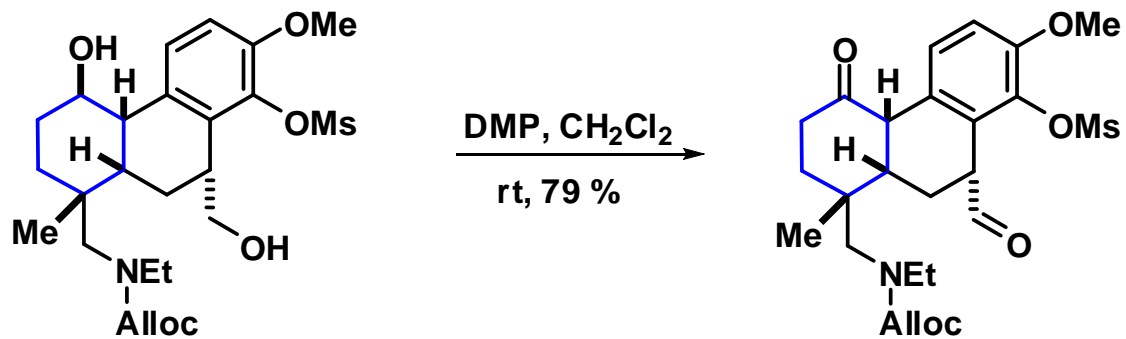


BHT, PhCN (20 mM)
160 °C, 6 h, 90 %

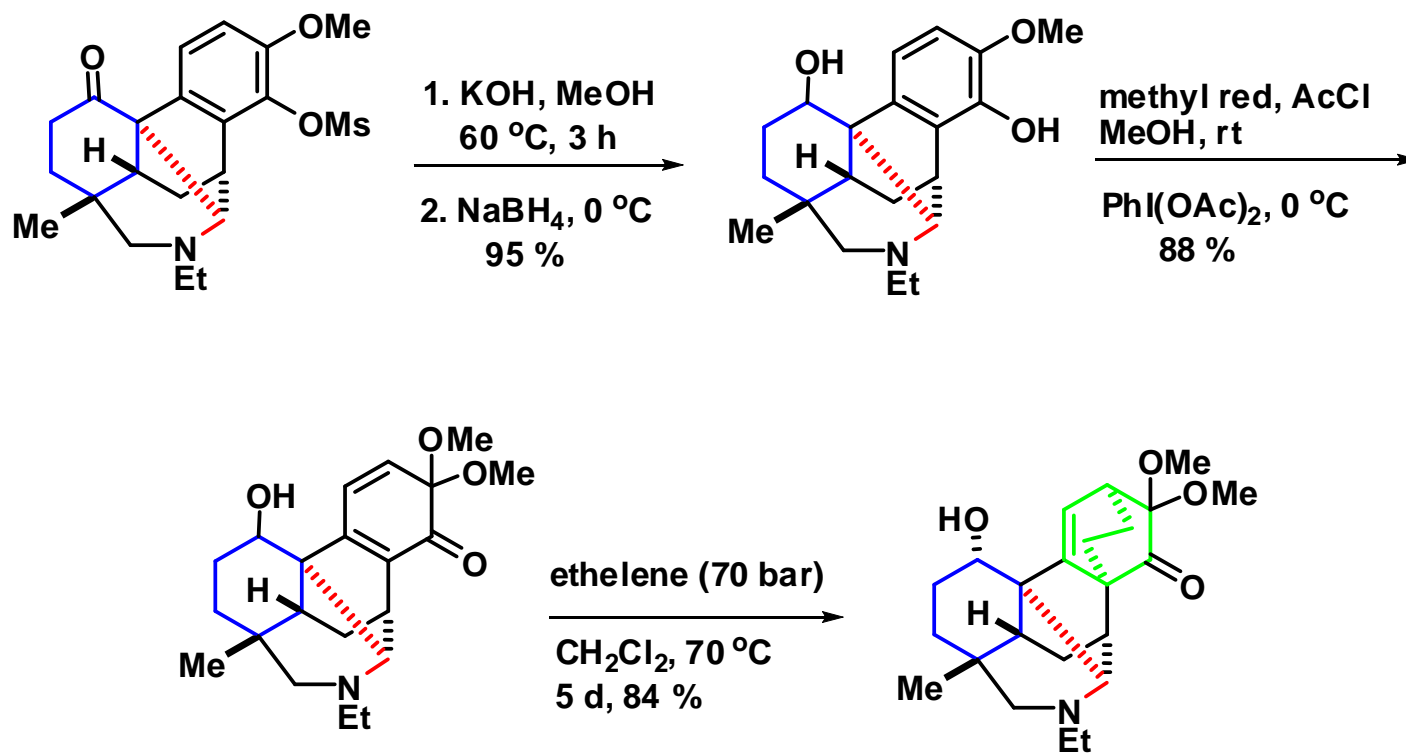


tethered Diels-Alder reaction

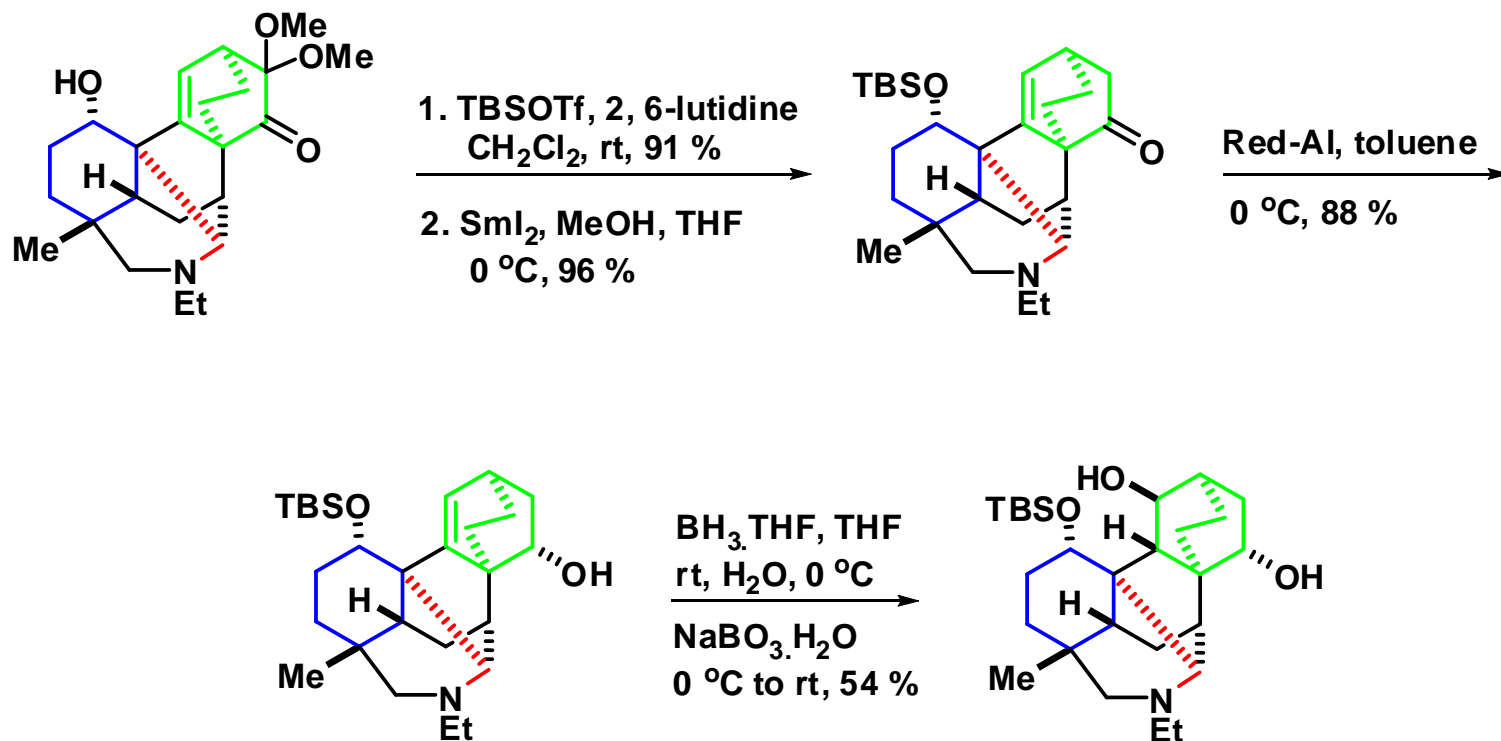




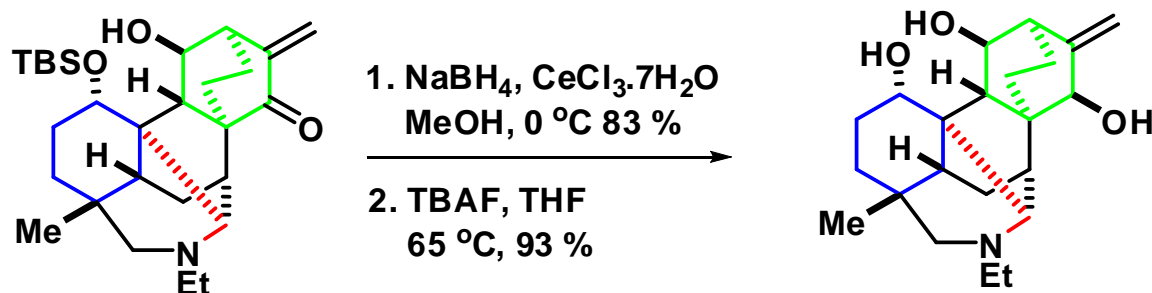
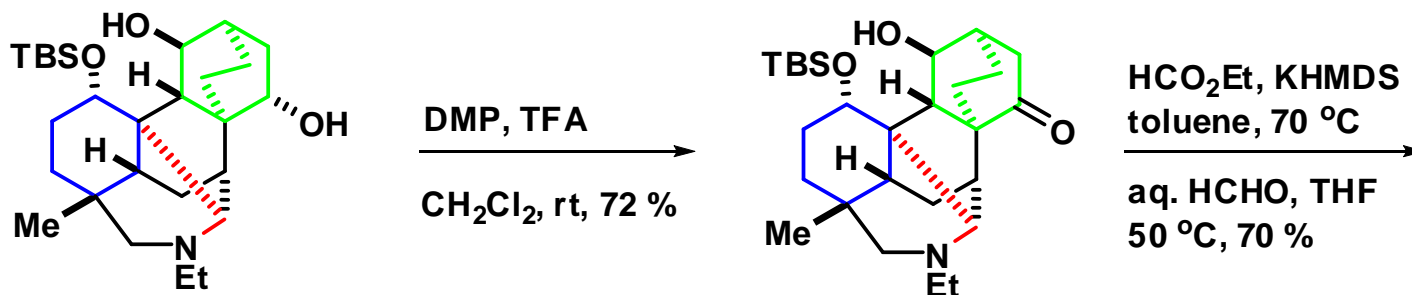
Intramolecular Mannich reaction



Intramolecular Diels-Alder reaction



End game of the synthesis



(-)-lepenine

Key features of the synthesis

1. Chirality transfer from L-lactic acid methyl ester via Claisen rearrangement
2. Construction of hexacyclic ring system via tethered intramolecular Diels-Alder reaction, Mannich reaction and Diels-Alder reaction between an *ortho*-quinone and ethylene

Thank you
For your attention

