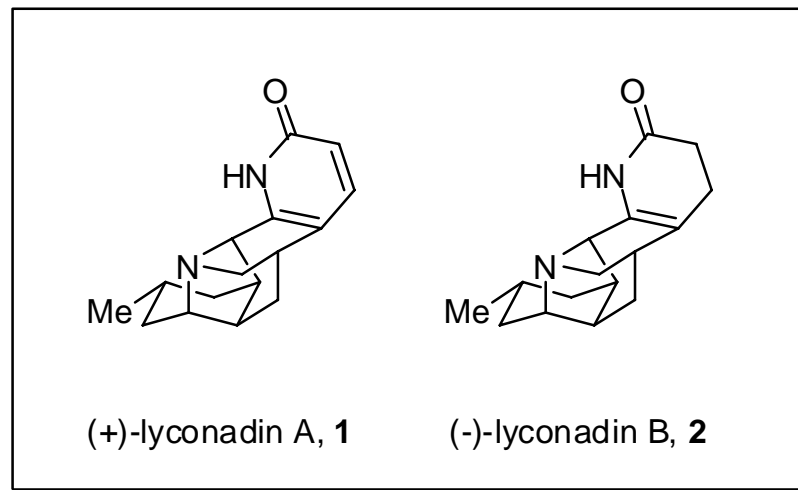


Total Syntheses of (+)- Lyconadin A and (-)-Lyconadin B

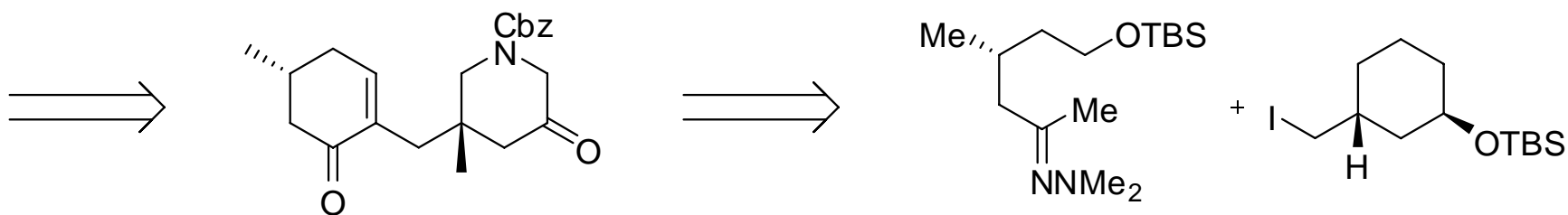
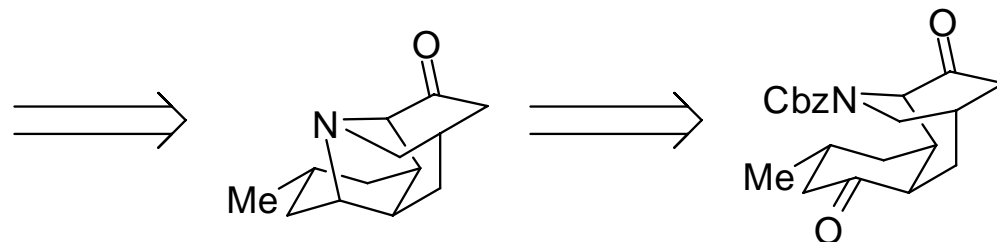
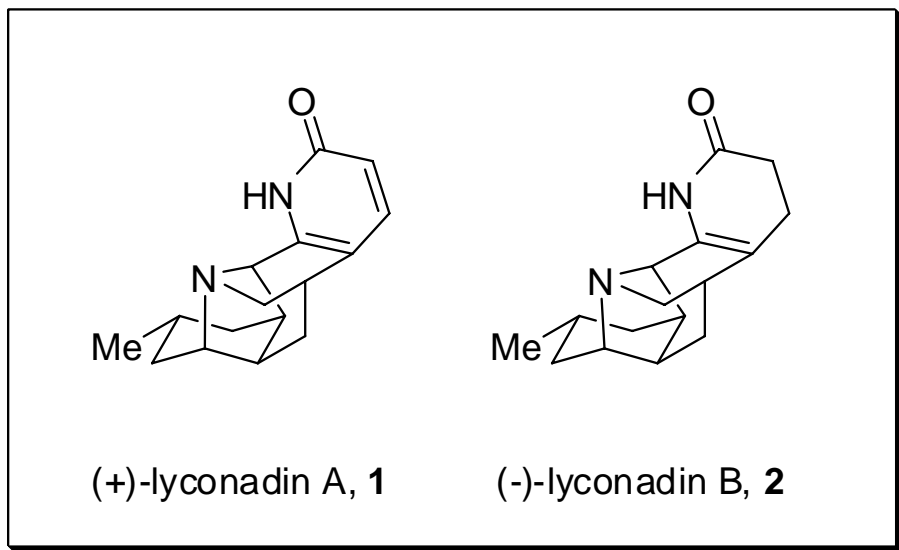
Lizzie O'Bryan
June 20, 2007
Literature Group Meeting

Background

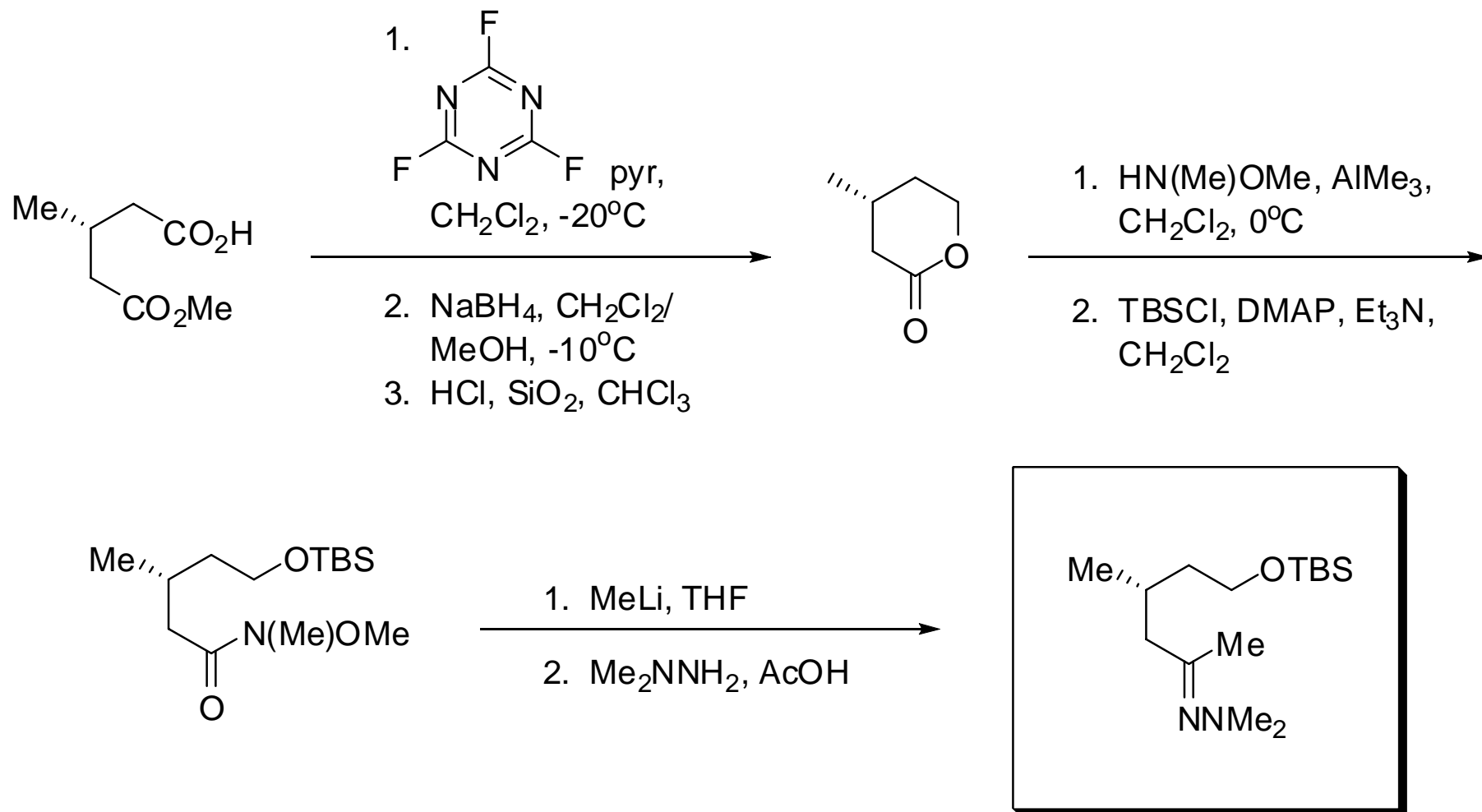
- (+)-Lyconadin A and (-)-lyconadin B were isolated by Kobayashi and coworkers in 2001 and 2006 respectively
- Isolated from club moss *Lycopodium complanatum*
- Lyconadin A possesses modest anticancer activity.
- Smith's is the first reported total synthesis of these alkaloids.



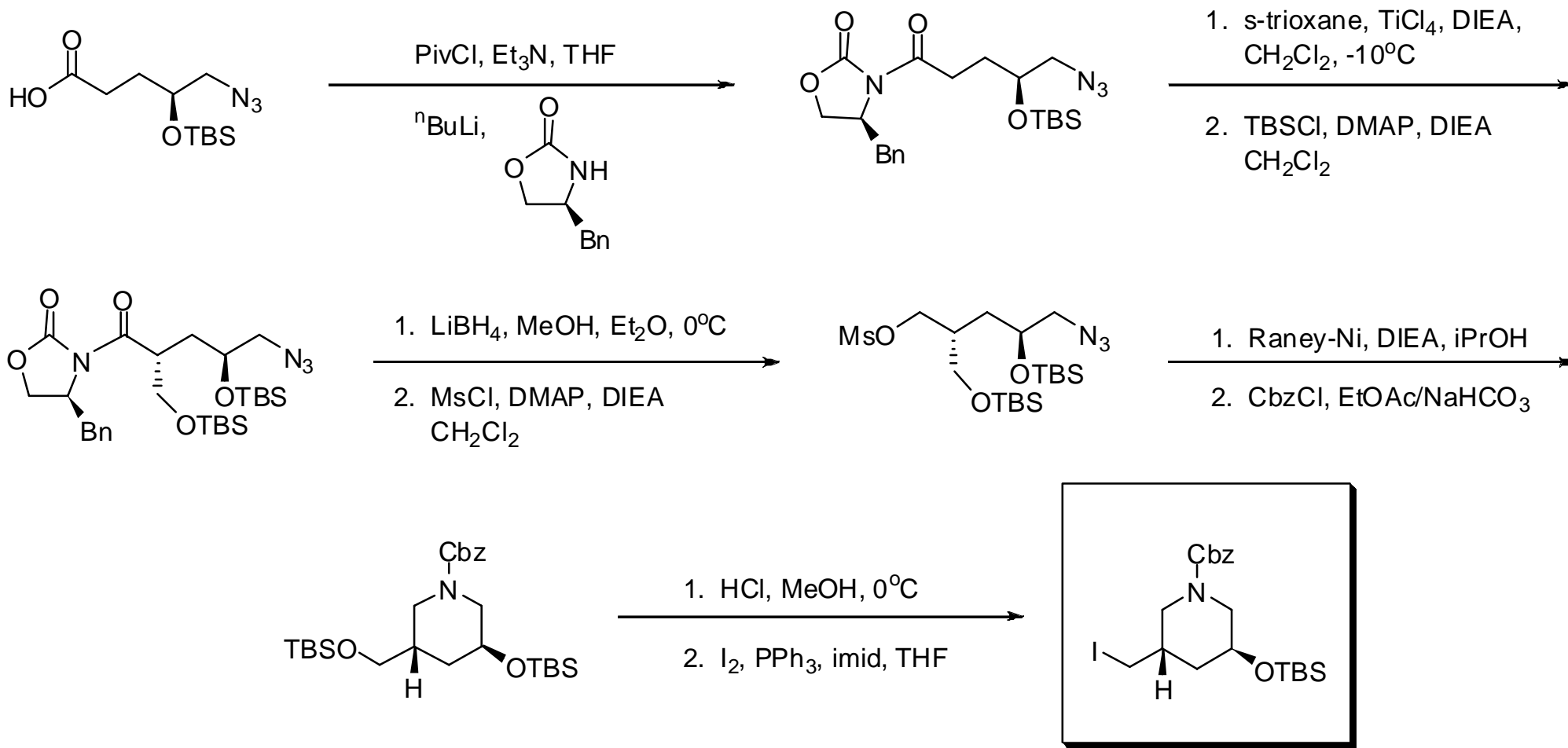
Smith's Retrosynthesis



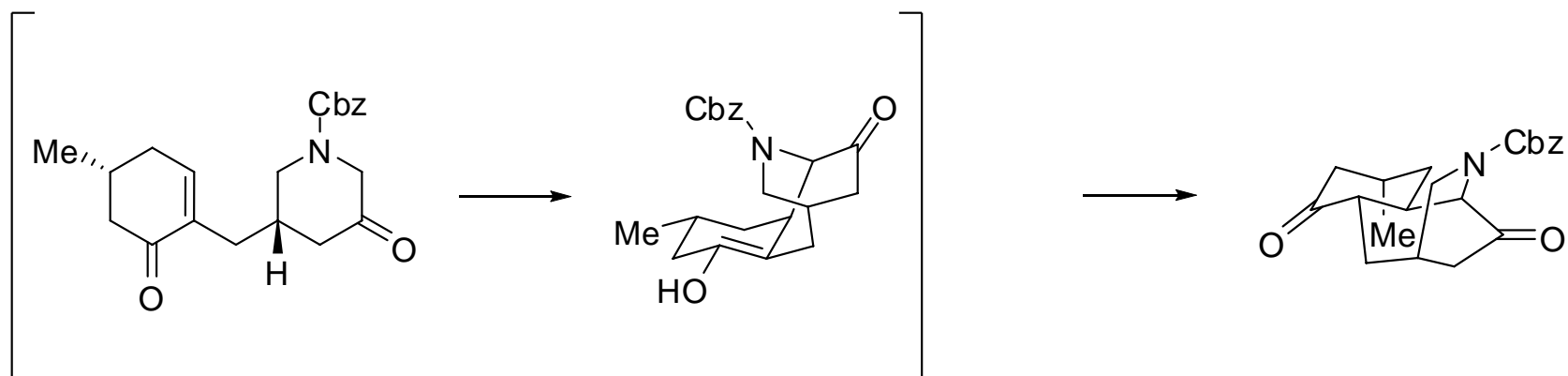
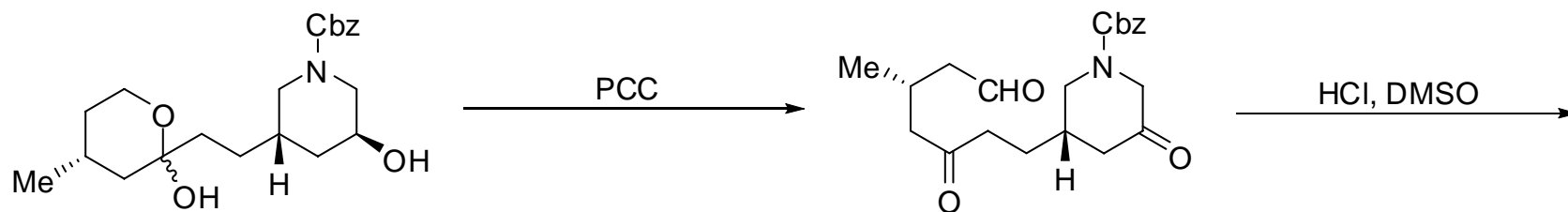
Synthesis of the Hydrazone



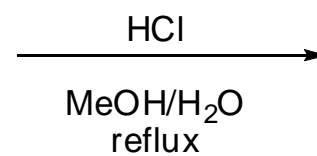
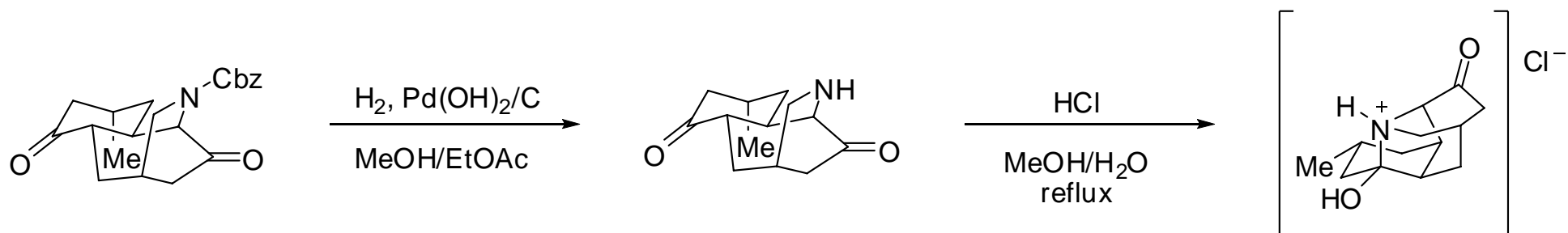
Synthesis of the Iodide



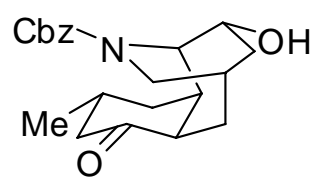
Coupling of the Hydrazone and Iodide



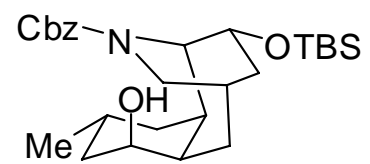
Synthesis of the Tetracyclic Core



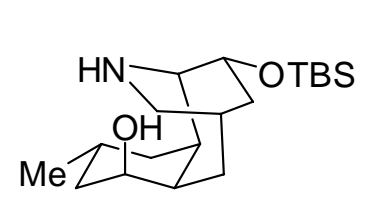
1. NaBH_4 , MeOH
2. CbzCl , $\text{EtOAc}/\text{NaHCO}_3$, CH_2Cl_2



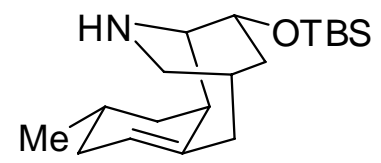
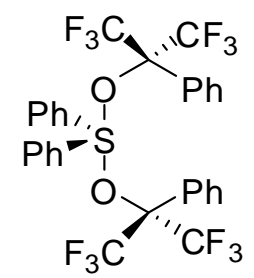
1. TBSOTf , DtBMP , CH_2Cl_2
2. L-selectride , CH_2Cl_2



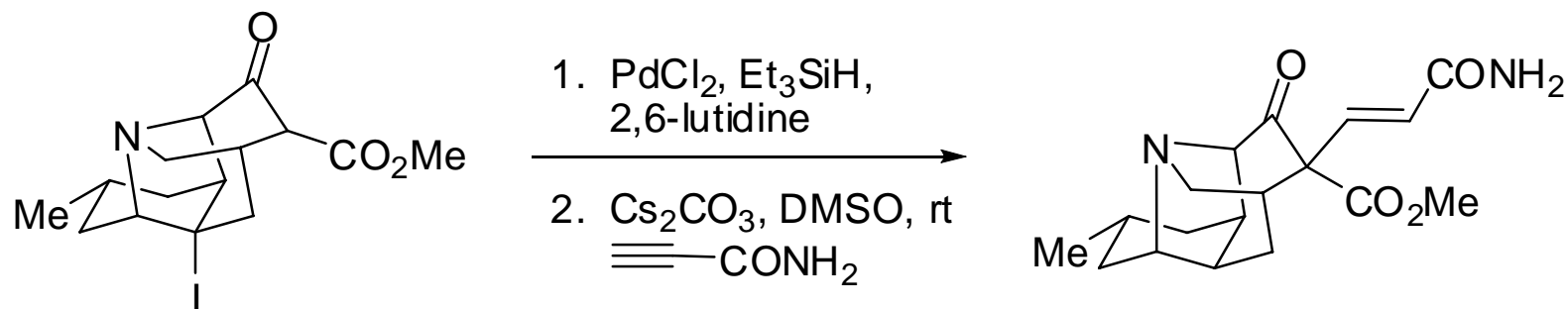
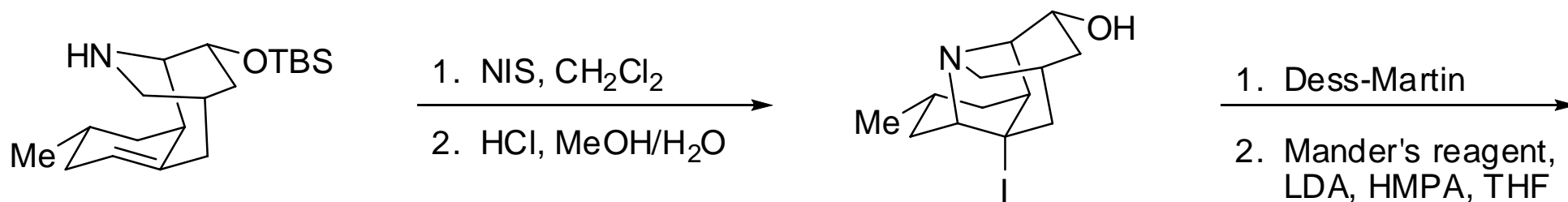
- Reagents: H_2 , Pd/C , EtOH



- Reagents: Martin sulfurane, CH_2Cl_2

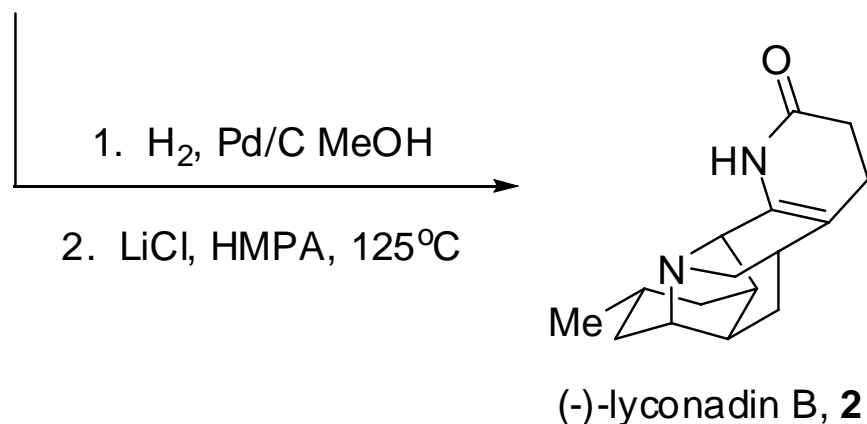
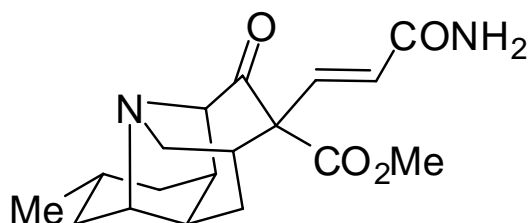
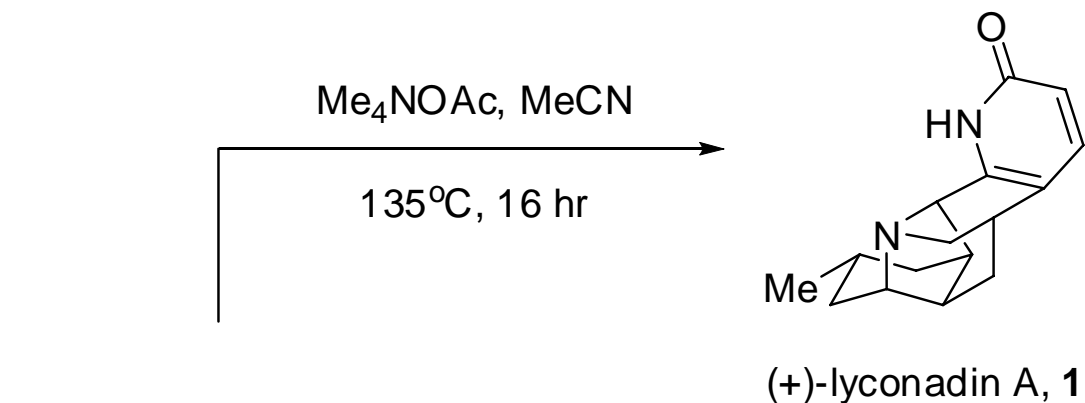


Synthesis of the Tetracyclic Core (cont)



Tet. Lett. **1983**, 24, 5425.
JOC, **1998**, 63, 5050.
JACS, **1980**, 102, 4743.

End Game



- Completion of (+)-Lyconadin A involved a one-pot decarboxylation, mediated by Me₄NOAc, olefin isomerization, and condensation to arrive at the natural product.

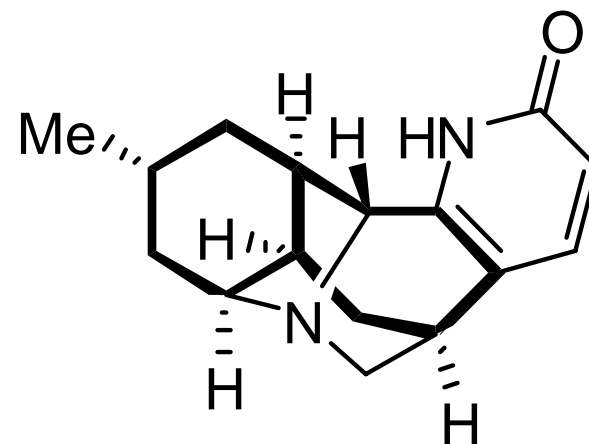
- (-)-Lyconadin B was accessed in a similar fashion following hydrogenation, with LiCl used to mediate the decarboxylation.

Summary of Smith's Synthesis

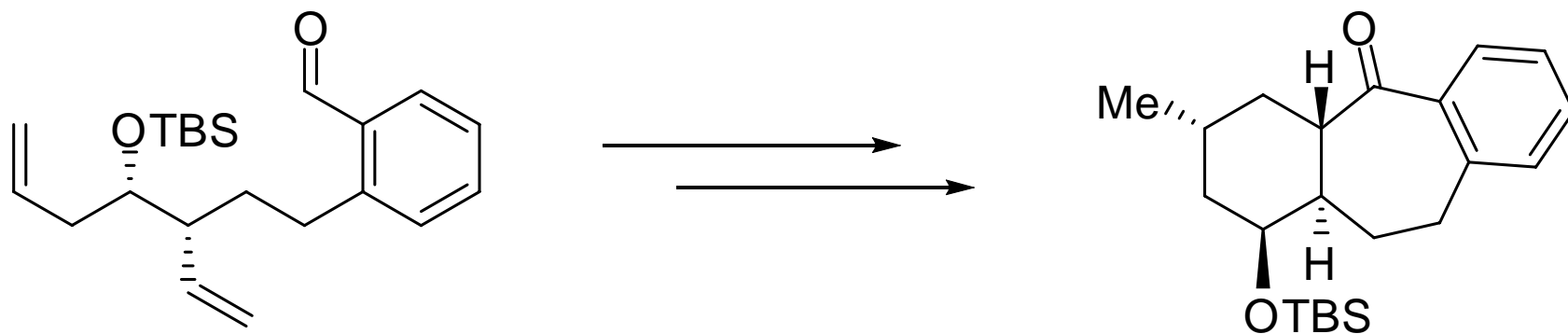
- Completed first total synthesis of (+)-Lyconadin A and (-)-Lyconadin B from a common advanced intermediate
- Key step was in the formation of the tricyclic ring system via an intramolecular aldol/conjugate addition cascade

Castle's Partial Synthesis

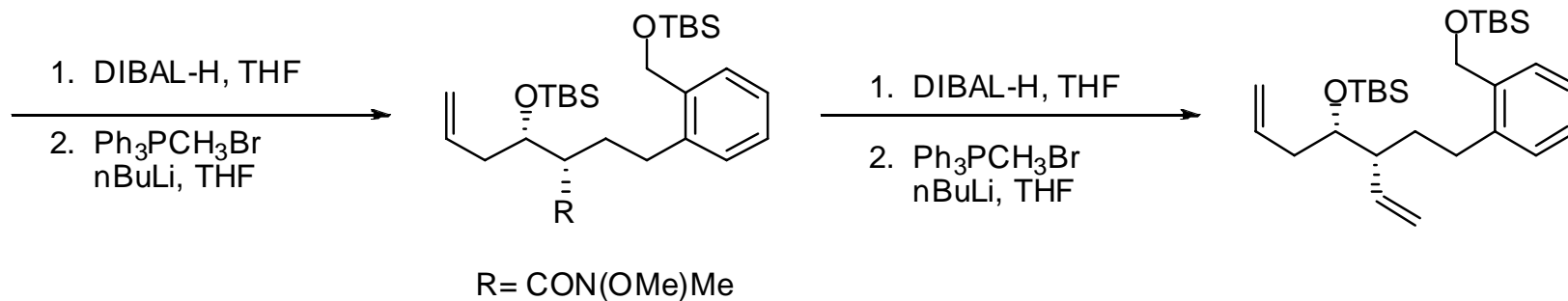
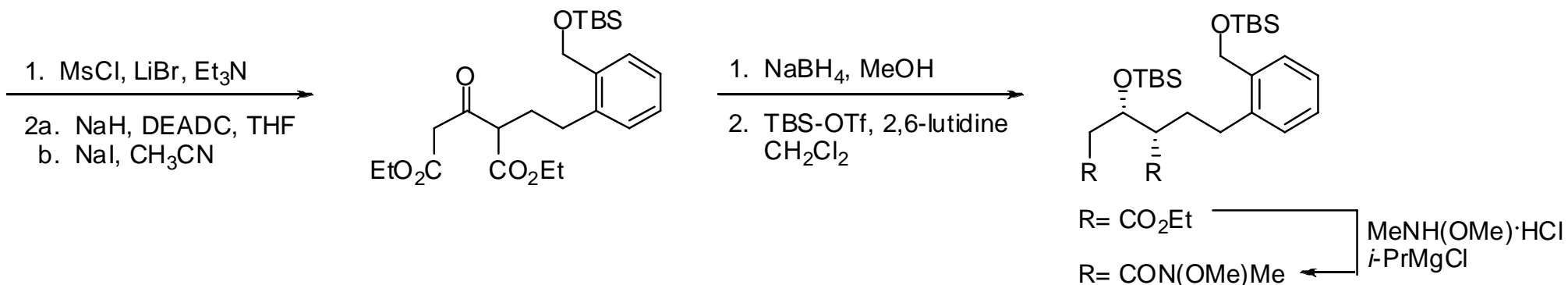
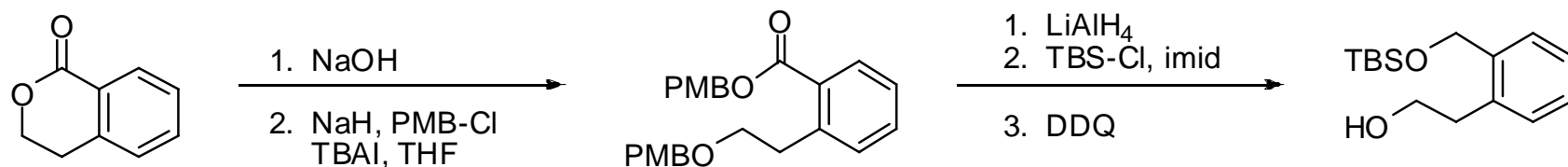
- Envisioned forming 6 and 7 membered rings of Lyconadin A via a tandem radical cyclization.
- Explore feasibility of this approach for Lyconadin A with model system.



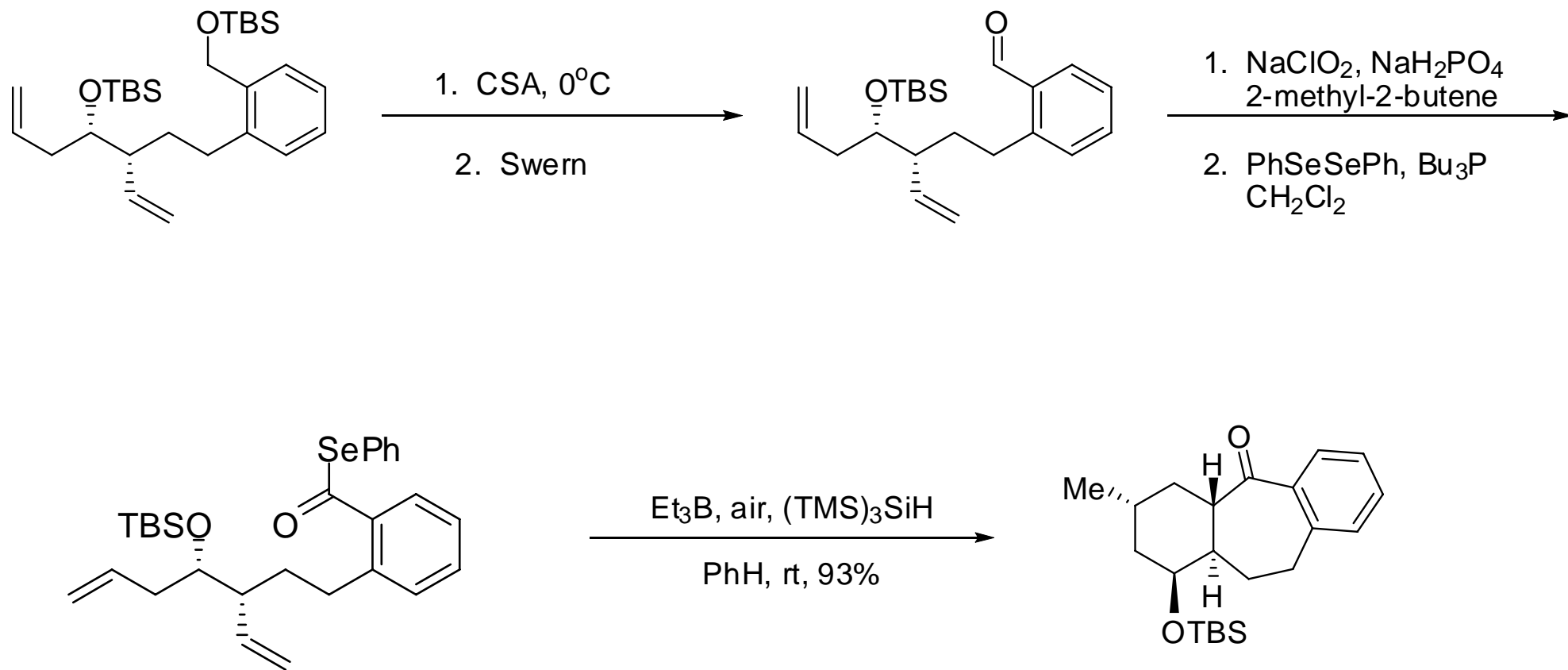
Model system for 7-exo-6-exo acyl radical cyclization:



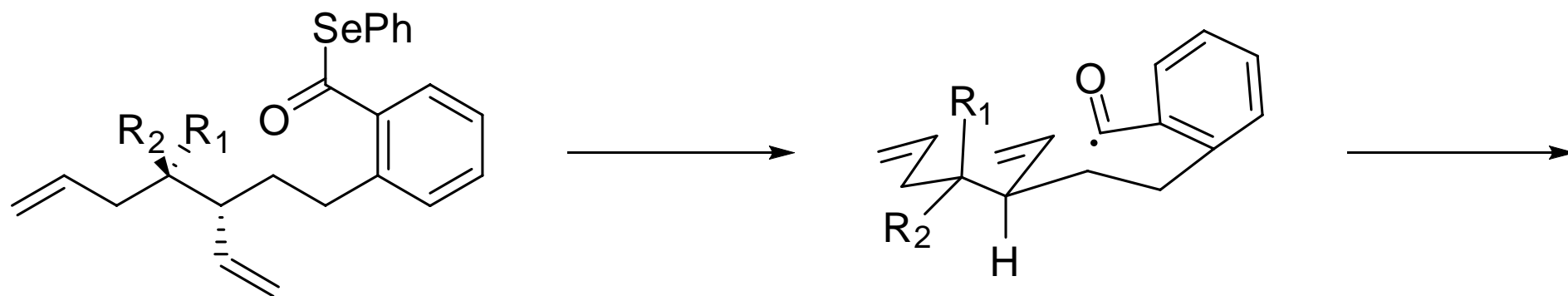
Synthesis of the Model System



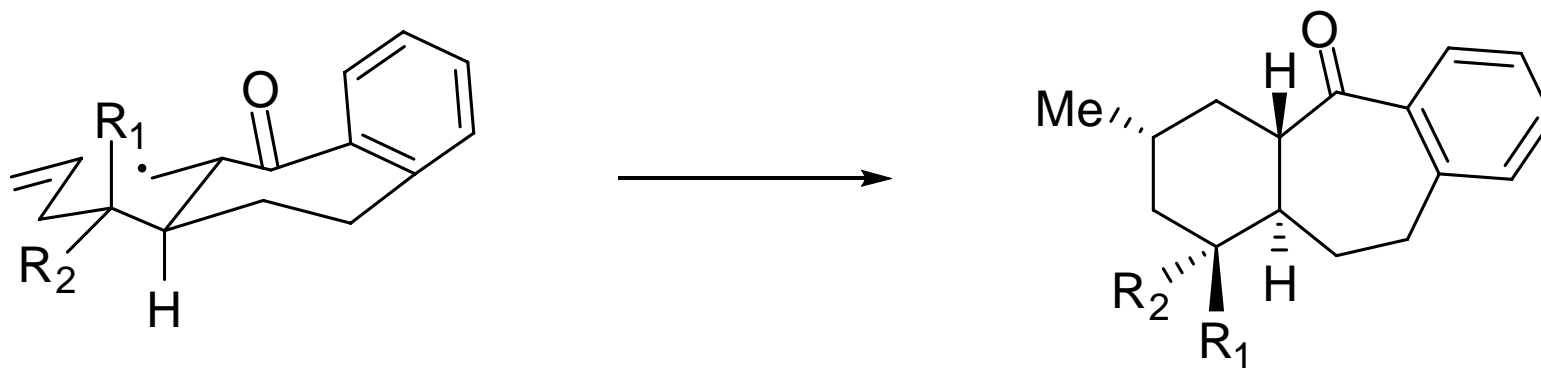
Synthesis of the Model System (cont)



Proposed Pathway for Tandem Cyclization

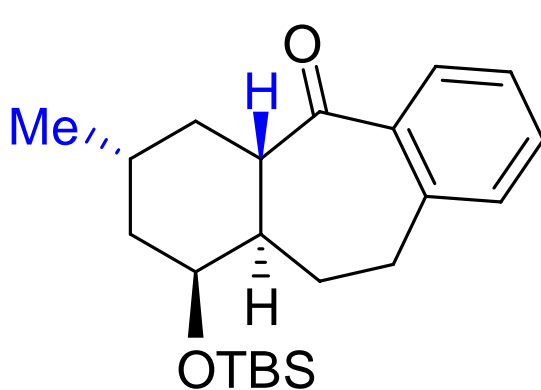


$R_1 = \text{OTBS}, R_2 = \text{H}$
 $R_1 = \text{OH}, R_2 = \text{H}$
 $R_1 = \text{H}, R_2 = \text{TBS}$

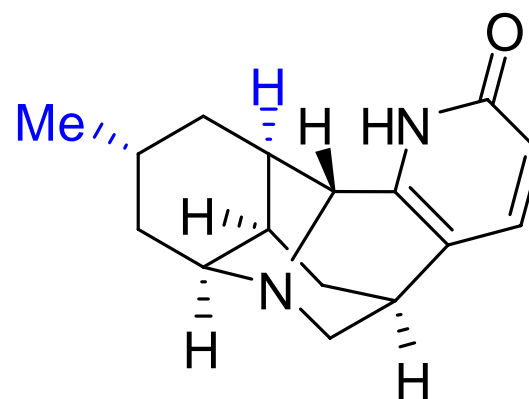


Summary of Castle's Efforts Towards Lyconadin A

- 7-exo-6-exo acyl radical cyclization provides correct stereochemistry for Lyconadin A at the methyl position, but not at the carbonyl ring junction α to the carbonyl
- Tandem cyclizations with and without TBS gave a single diastereomer.



Model system



Lyconadin A