Asymmetric Total Synthesis of Kopsiyunnanine K, a Monoterpenoid Indole Alkaloid with a Rearranged Skeleton

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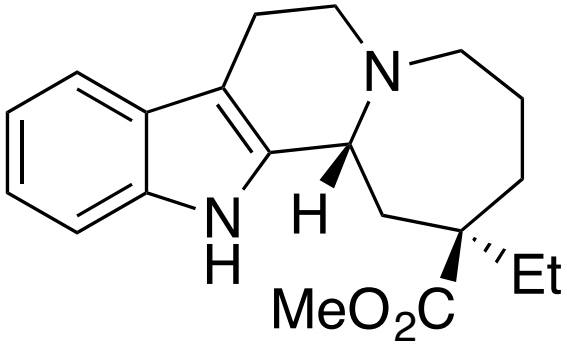
I. Introduction

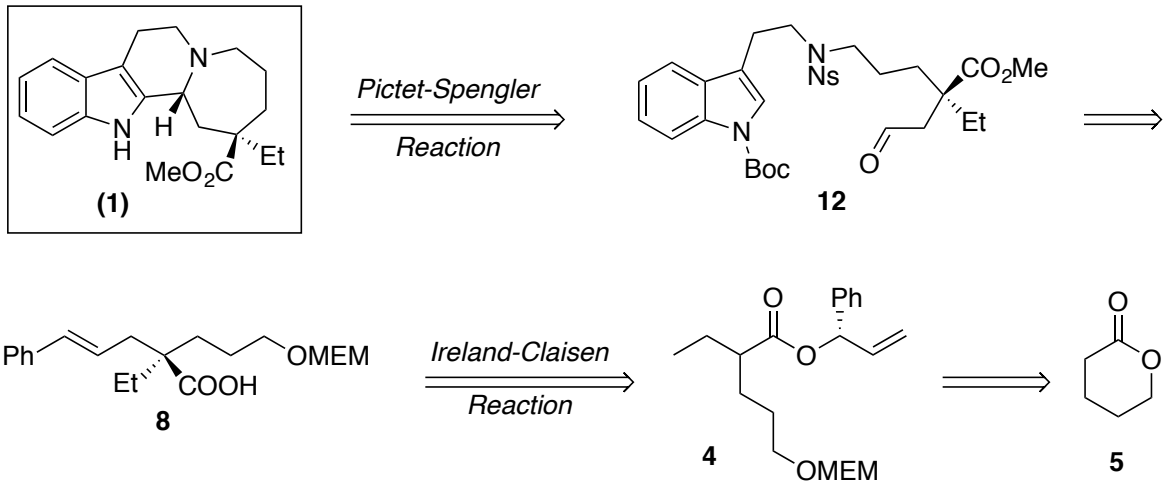
- Isolated from *Kopsia arborea*, a tree native to the Yunnan Province in China
- Total synthesis executed to clarify structure and absolute configuration of the compound
- Structural Features:
  - Unprecedented azepine-fused tetrahyro-*ß*-carboline ring skeleton
- 13 step synthesis



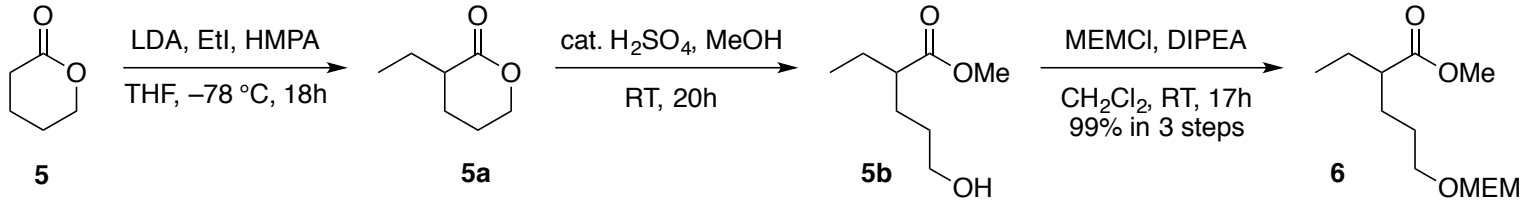
(1) Kopsiyunnanine K

Retrosynthetic Analysis of Kopsiyunnanine K

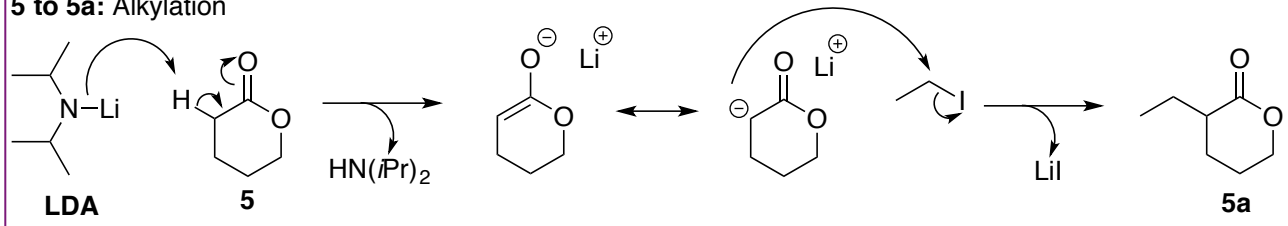
II. Retrosynthetic Analysis



III. Forward Synthesis

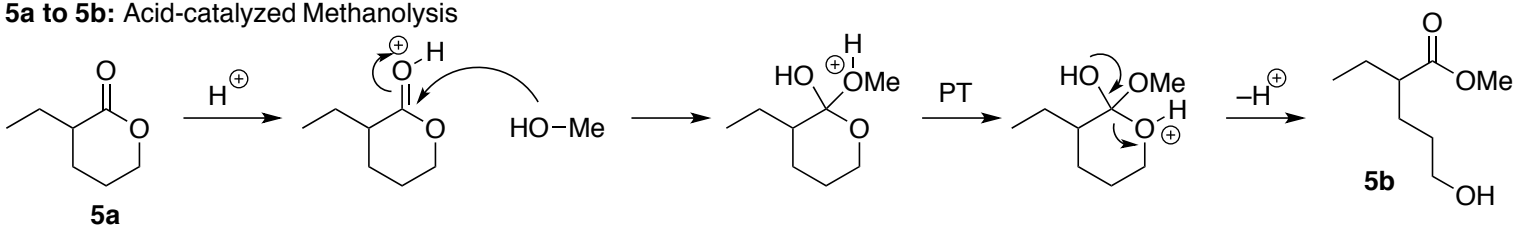


5 to 5a: Alkylation

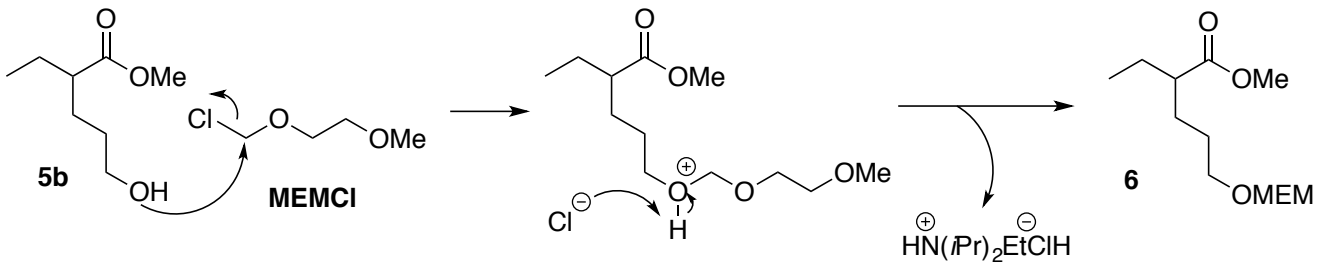


* HMPA sequesters Li^+ ion to accelerate SN2 reaction

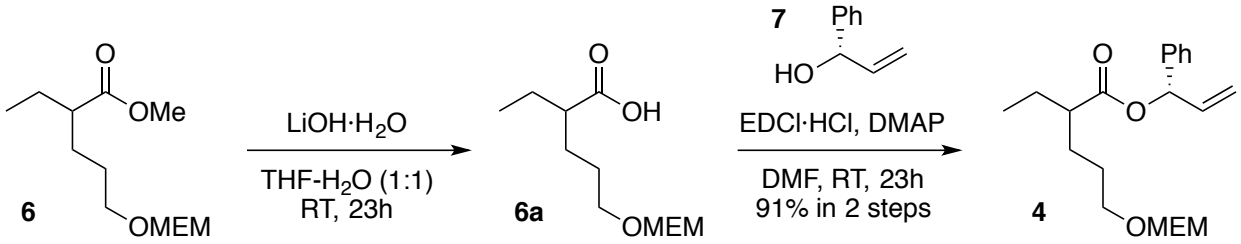
5a to 5b: Acid-catalyzed Methanolysis



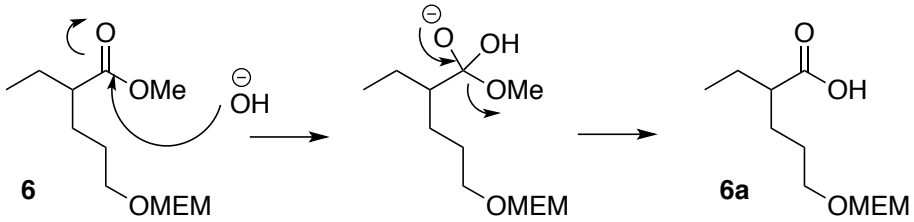
5b to 6: MEM protection



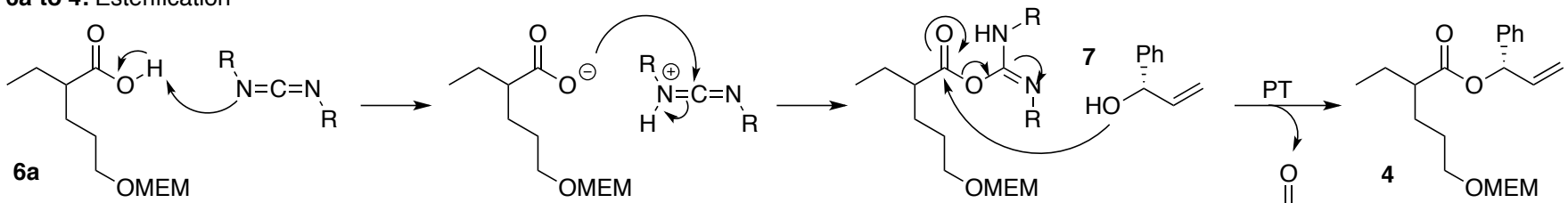
III. Forward Synthesis

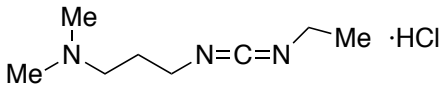


6 to 6a: Alkaline hydrolysis



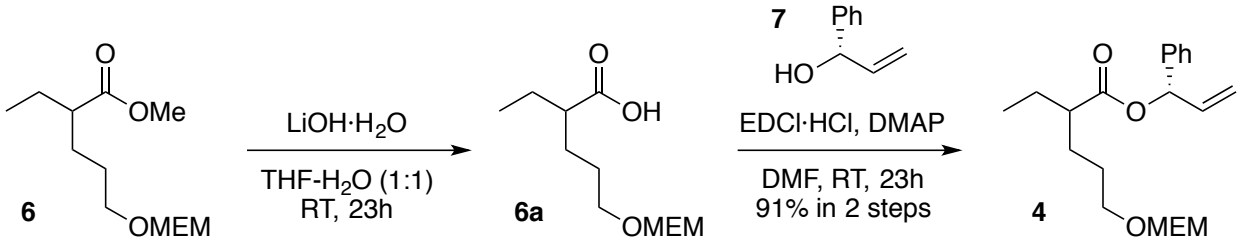
6a to 4: Esterification

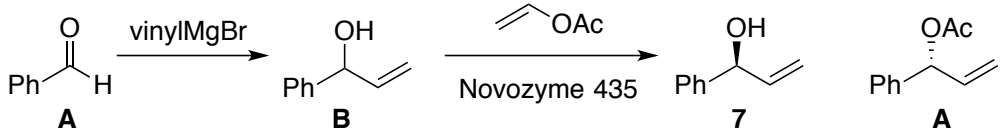




EDC·HCl

III. Forward Synthesis





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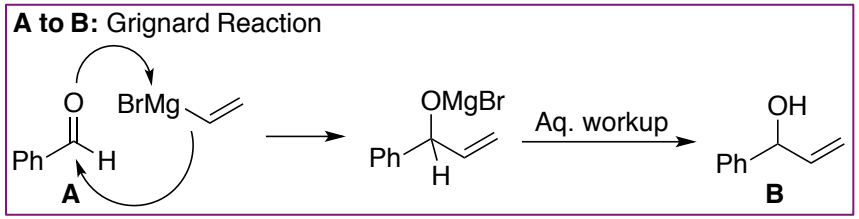
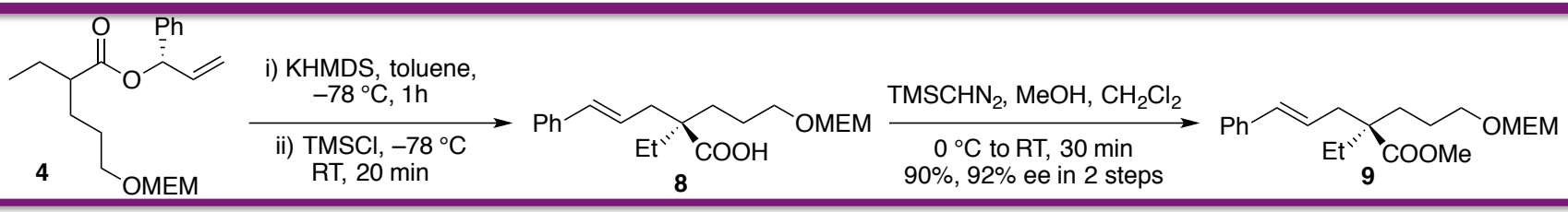
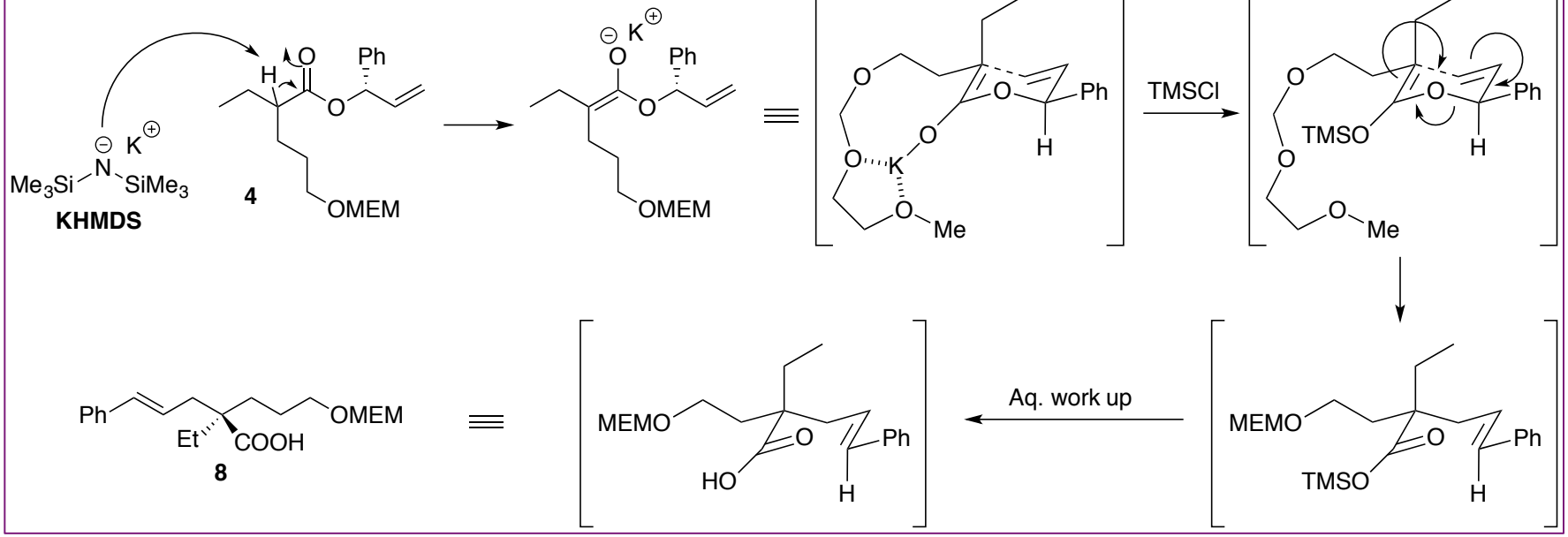


B to 7/A: Enzymatic Acylation – One enantiomer is acylated and the products can be separated

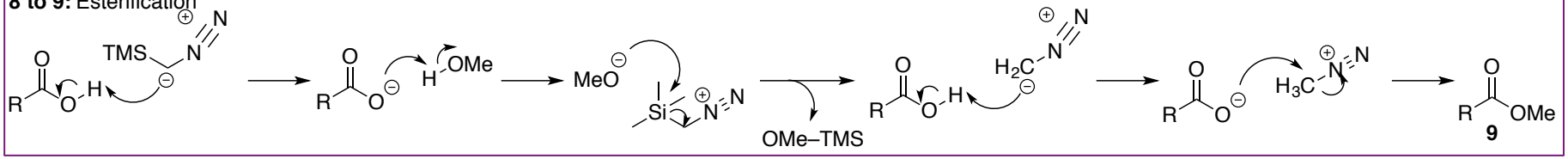
III. Forward Synthesis



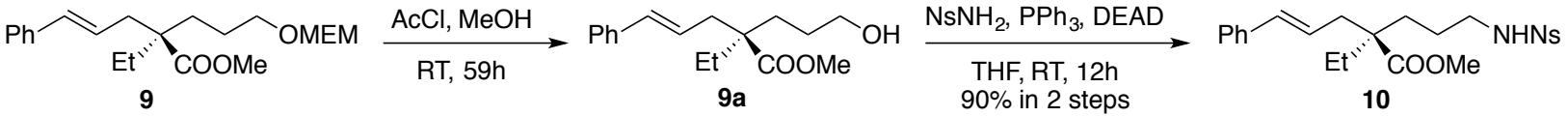
4 to 8: Ireland-Claisen Reaction



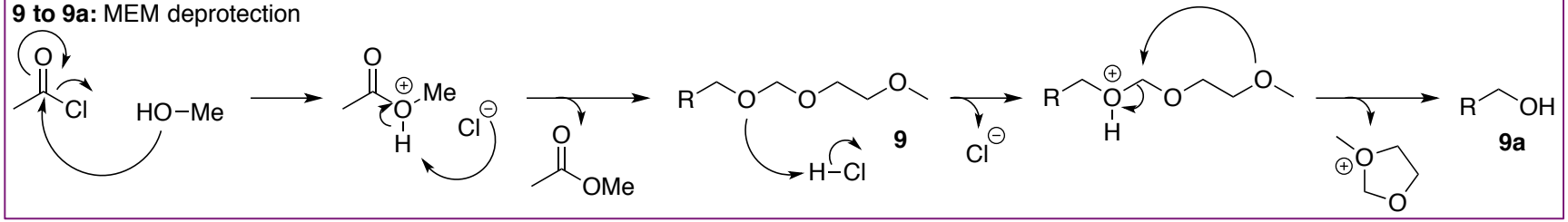
8 to 9: Esterification



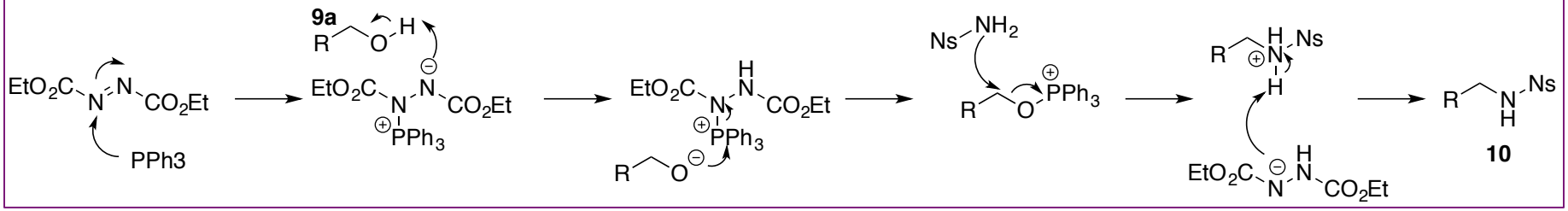
III. Forward Synthesis



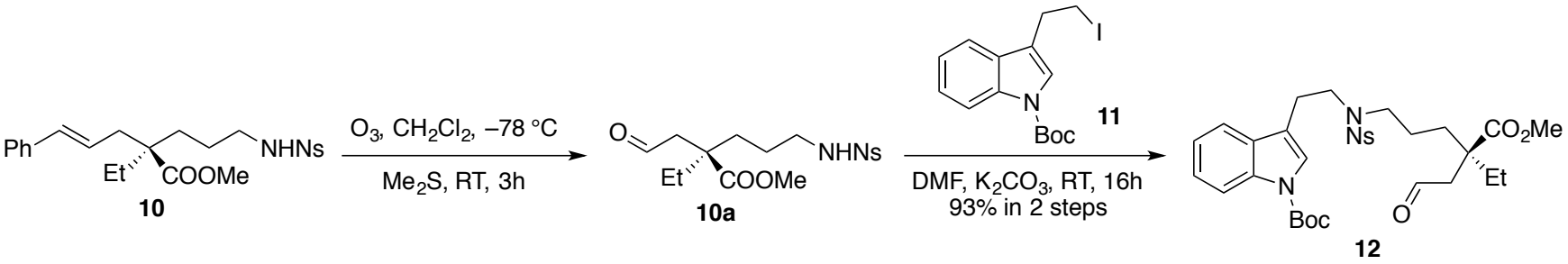
9 to 9a: MEM deprotection



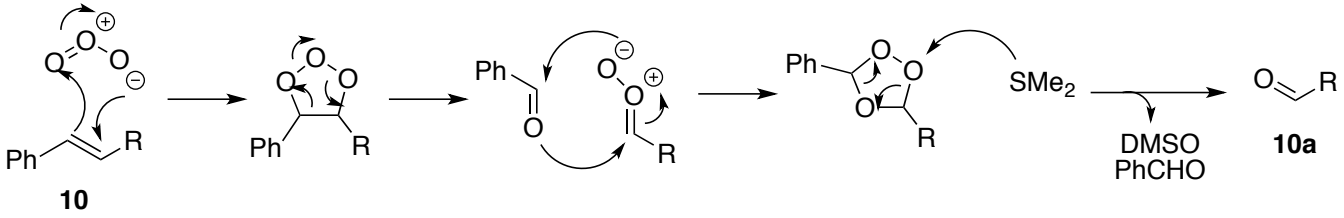
9a to 10: Mitsunobu Reaction



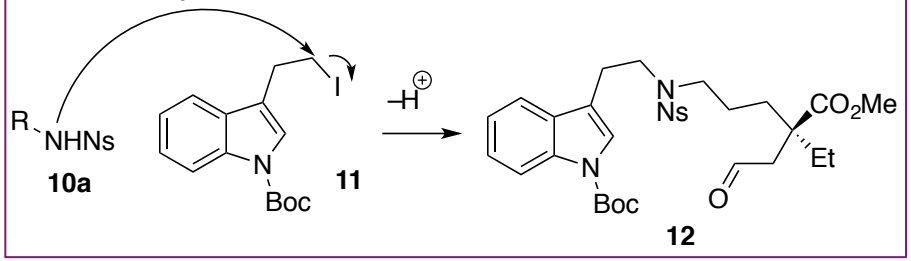
III. Forward Synthesis



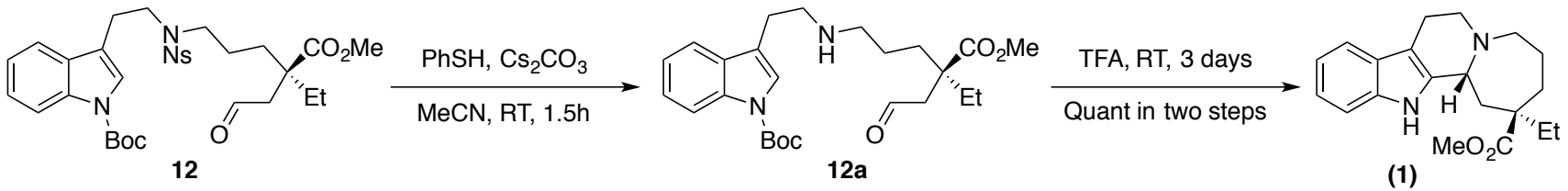
10 to 10a: Oxonolysis



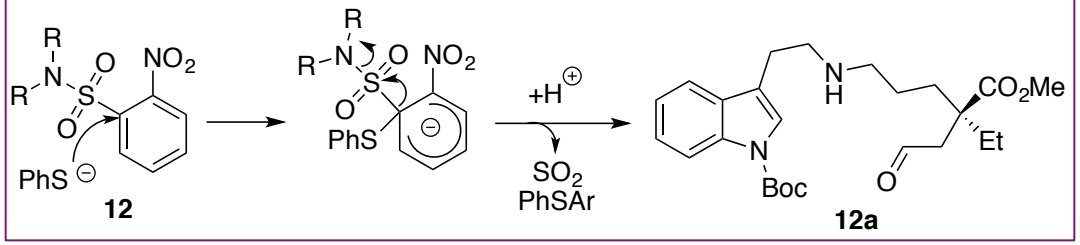
10a to 12: Alkylation



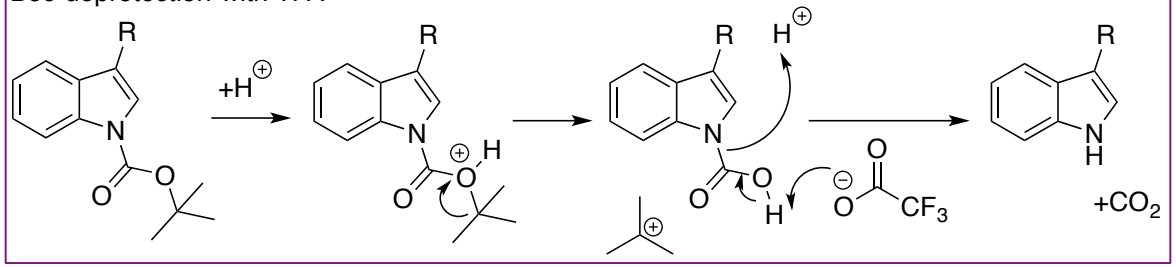
III. Forward Synthesis



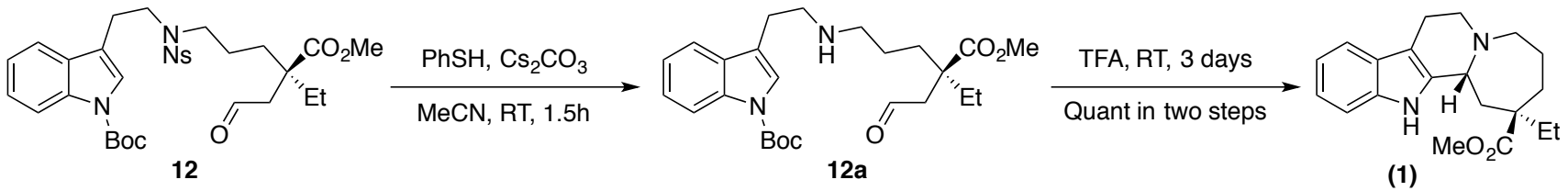
12 to 12a: Nosyl deprotection



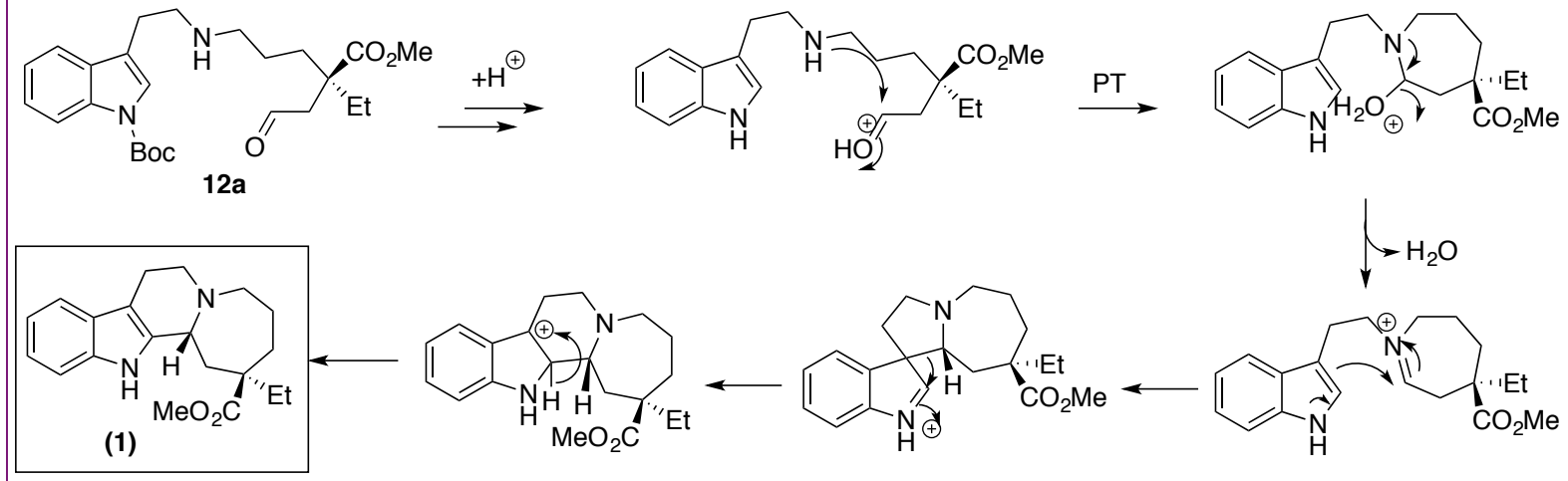
Boc-deprotection with TFA



III. Forward Synthesis



12a to 1: PIctet-Spengler Reaction



Recrystallization in
EtOAc/Et_2O
92% ee to 95% ee