

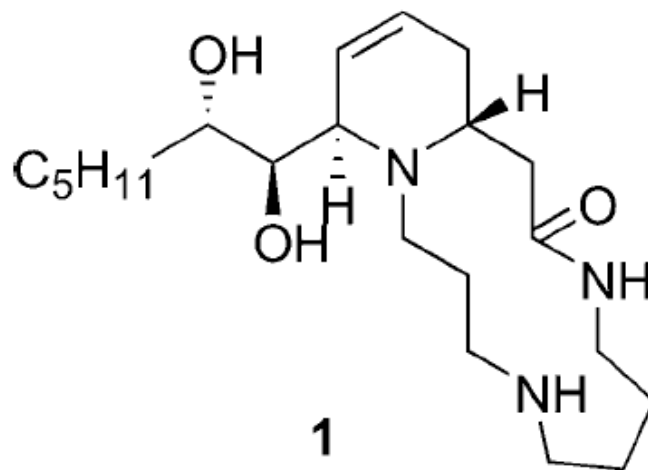
Asymmetric Total synthesis of (+)-Cannabisativine

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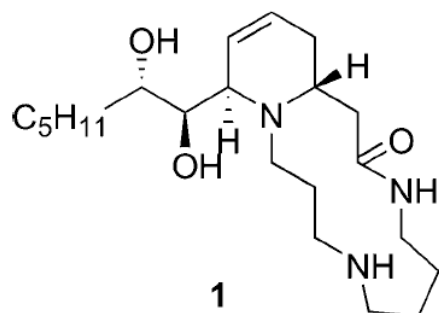


(+)-cannabisativine

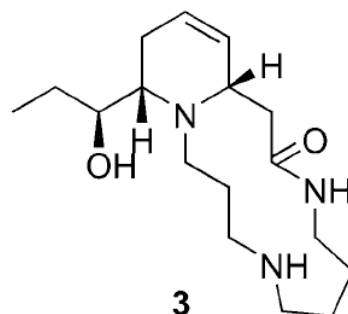
Kuethe, J. T.; Comins, D. L.; *J. Org. Chem.*; **2004**; 69(16); 5219-5231.

Kuethe, J. T.; Comins, D. L.; *Org. Lett.*; **2000**; 2(6); 855-857.

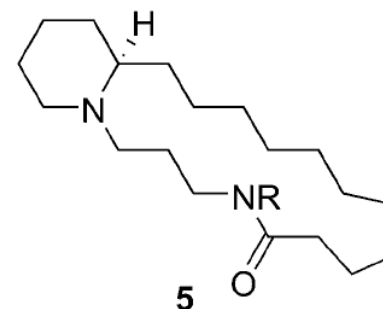
Naturally Occurring Macrocyclic Polyamine Alkaloids Containing Spermidine Subunits



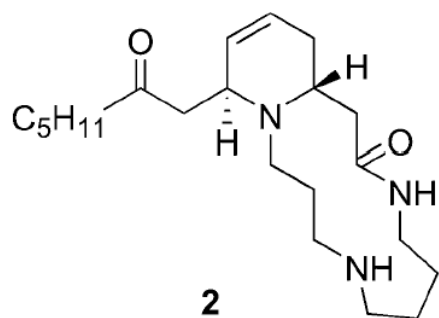
(+)-cannabisativine



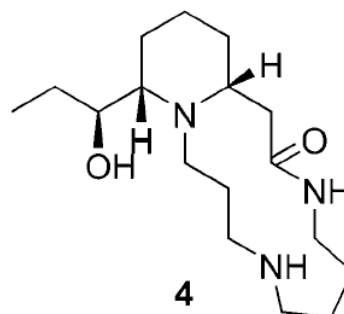
(+)-palustrine



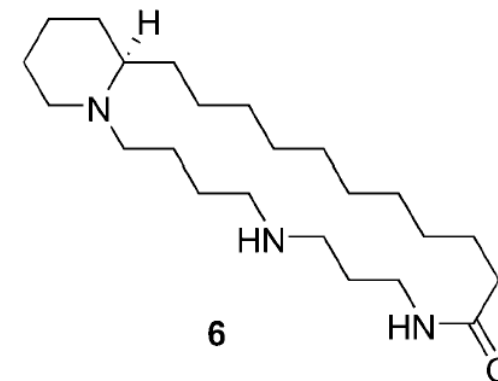
(-)-oncinotine
R = (CH₂)₄NH₂



anhydrocannabisativine

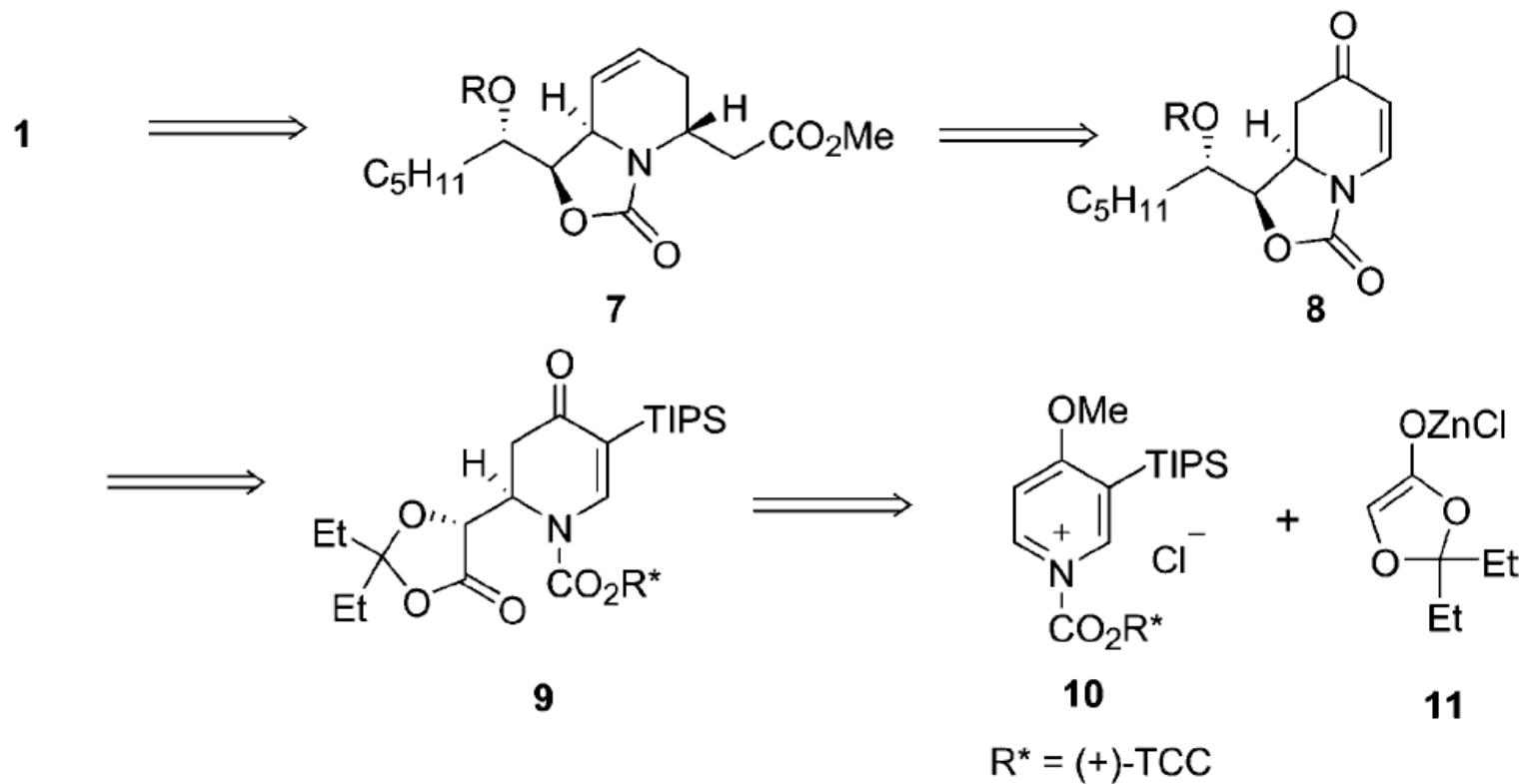


(+)-dihydropalustrine

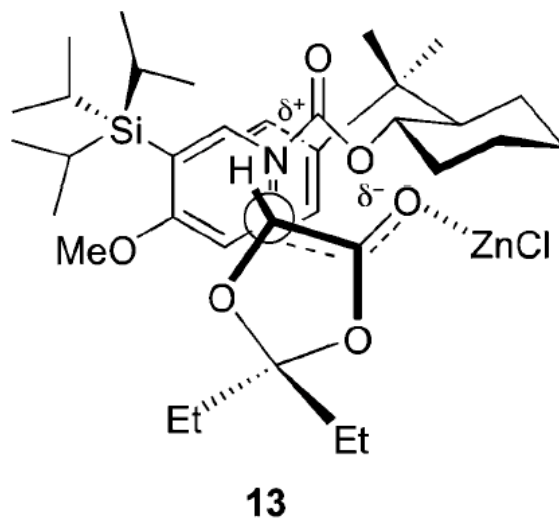
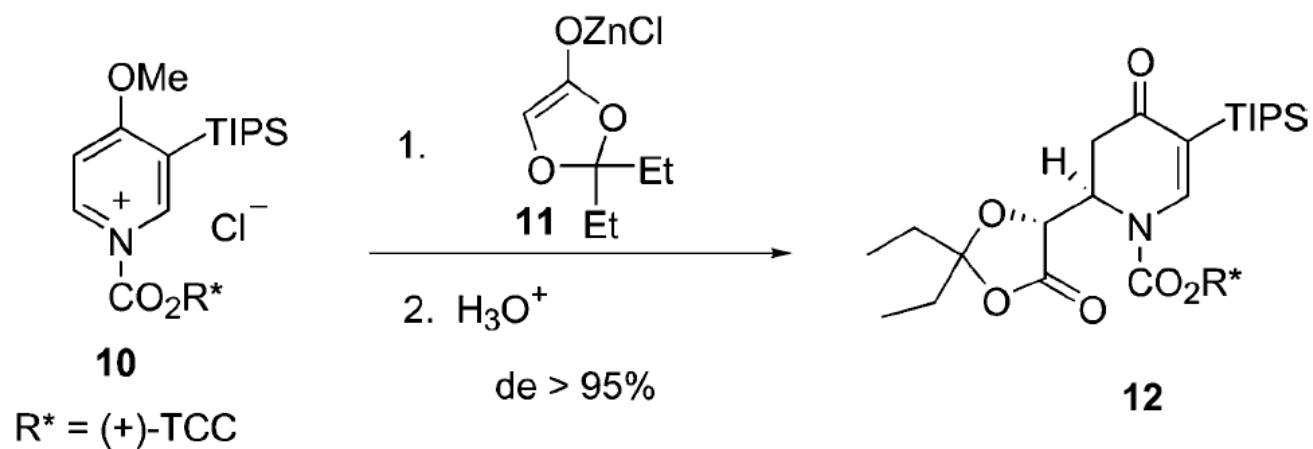


(-)-Isooncinotine

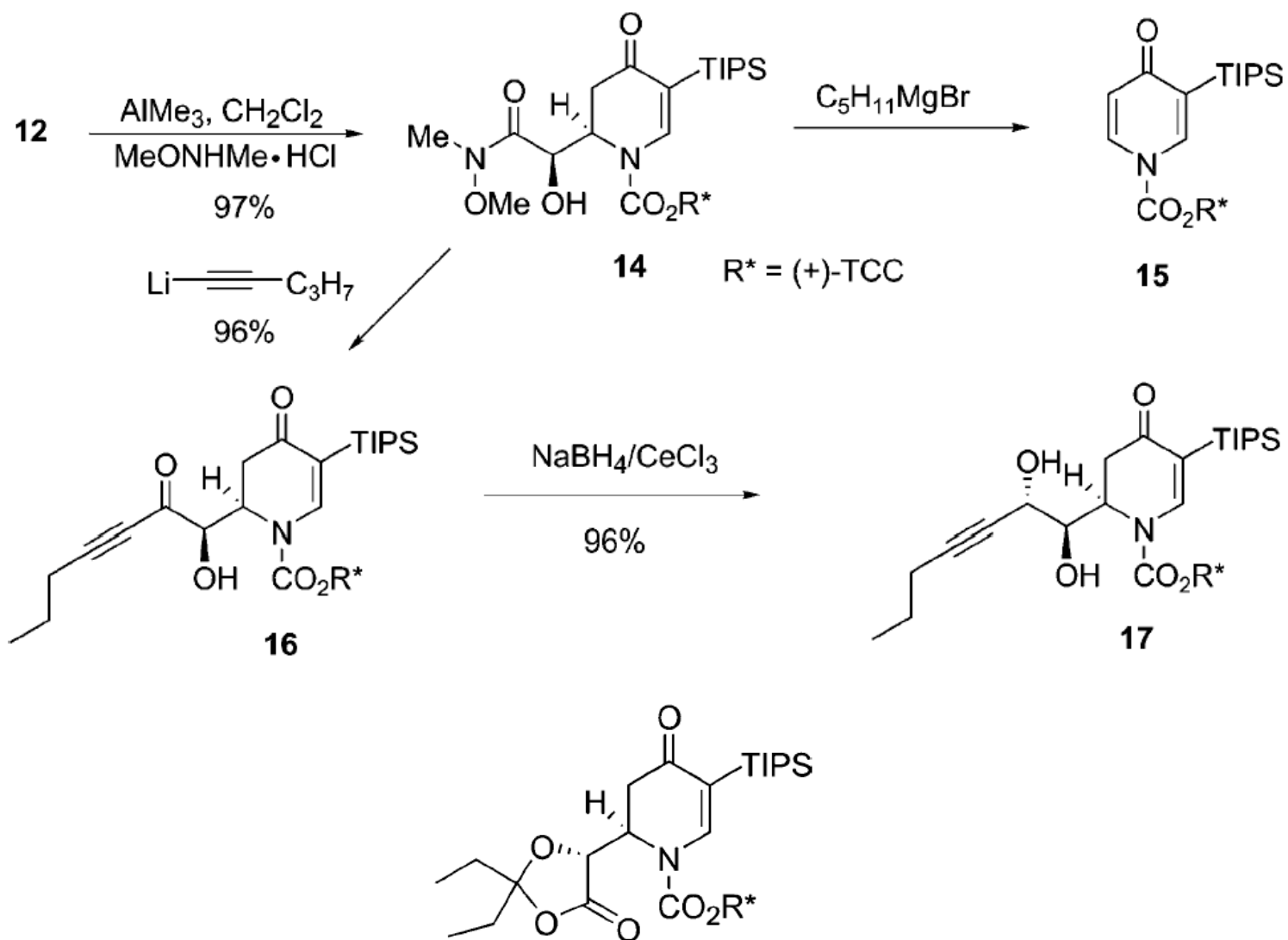
Retrosynthetic Approach to (+)-Cannabisativine



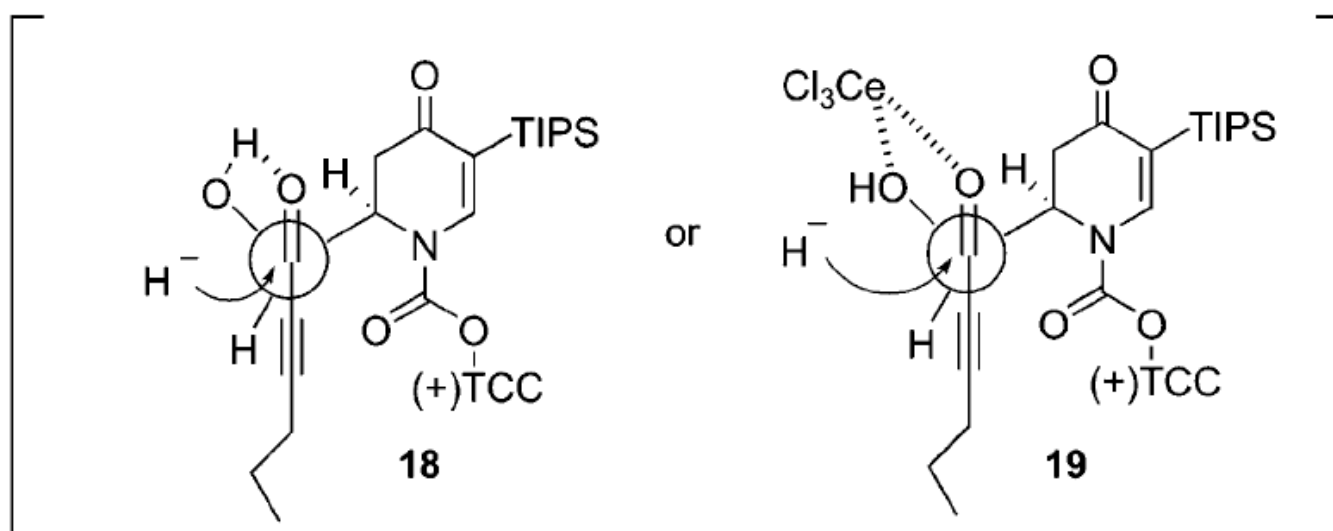
Preparation of Dihydropyridone **12**



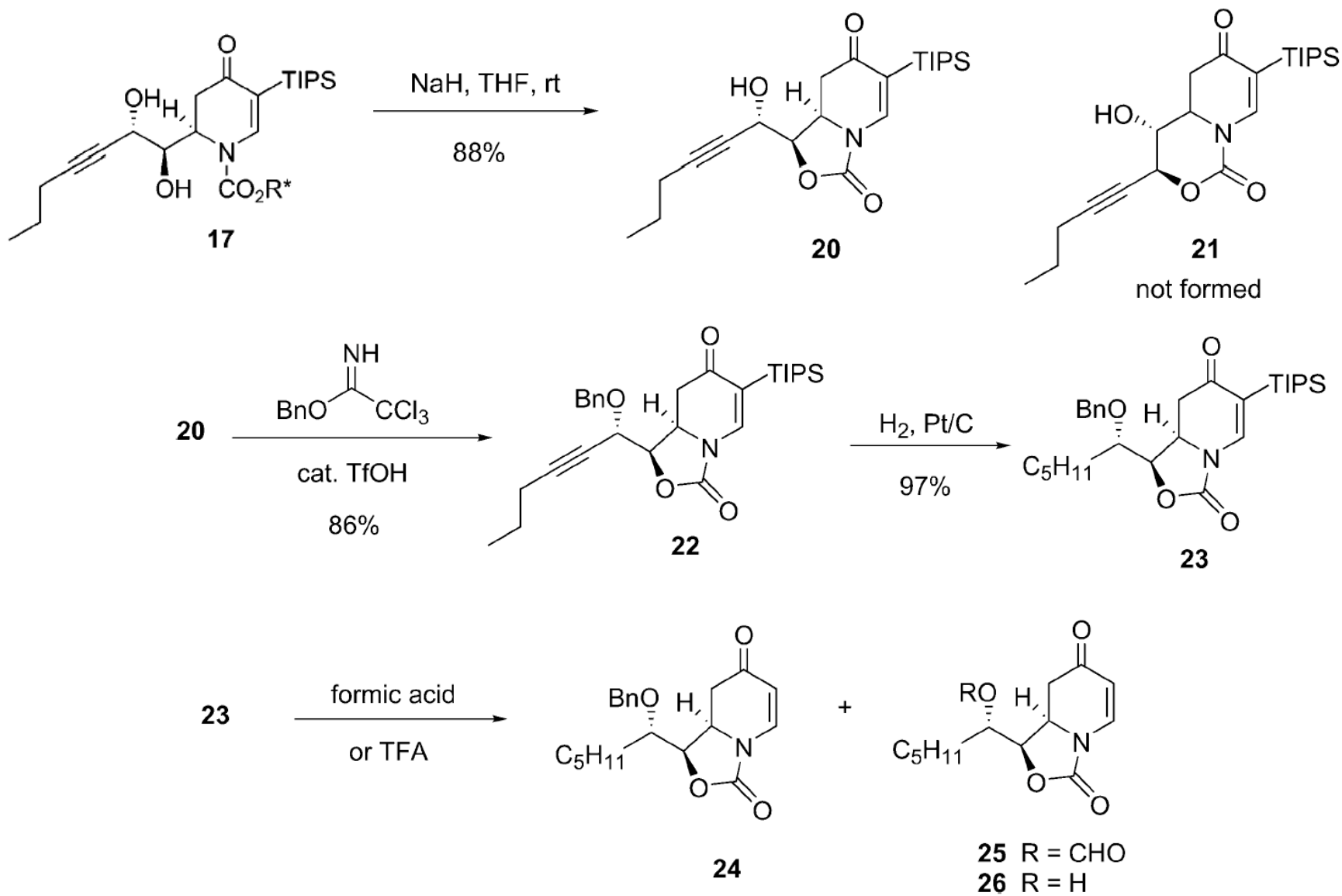
Preparation of Dihydropyridone 17



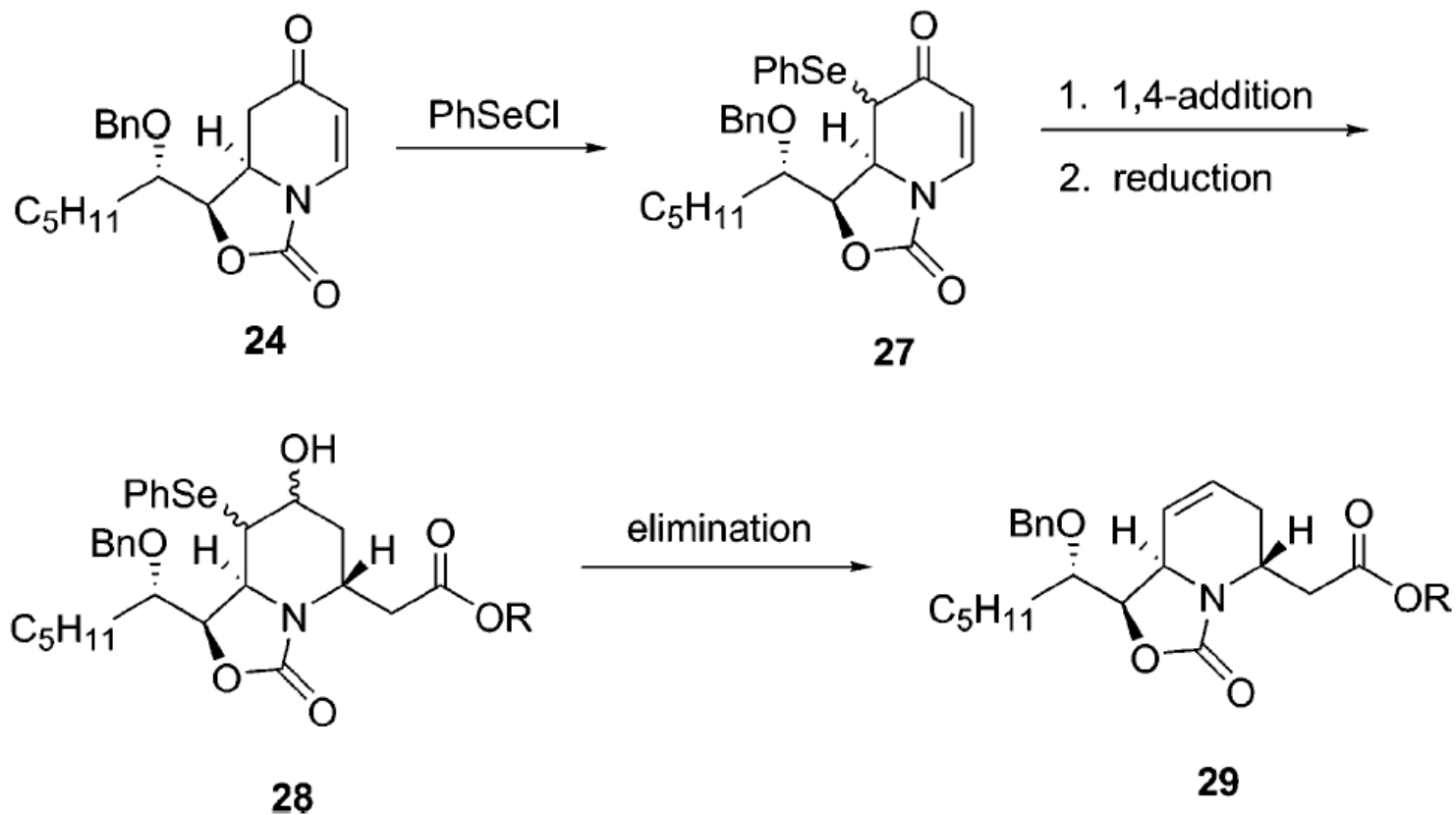
Lucho Reduction Transition States



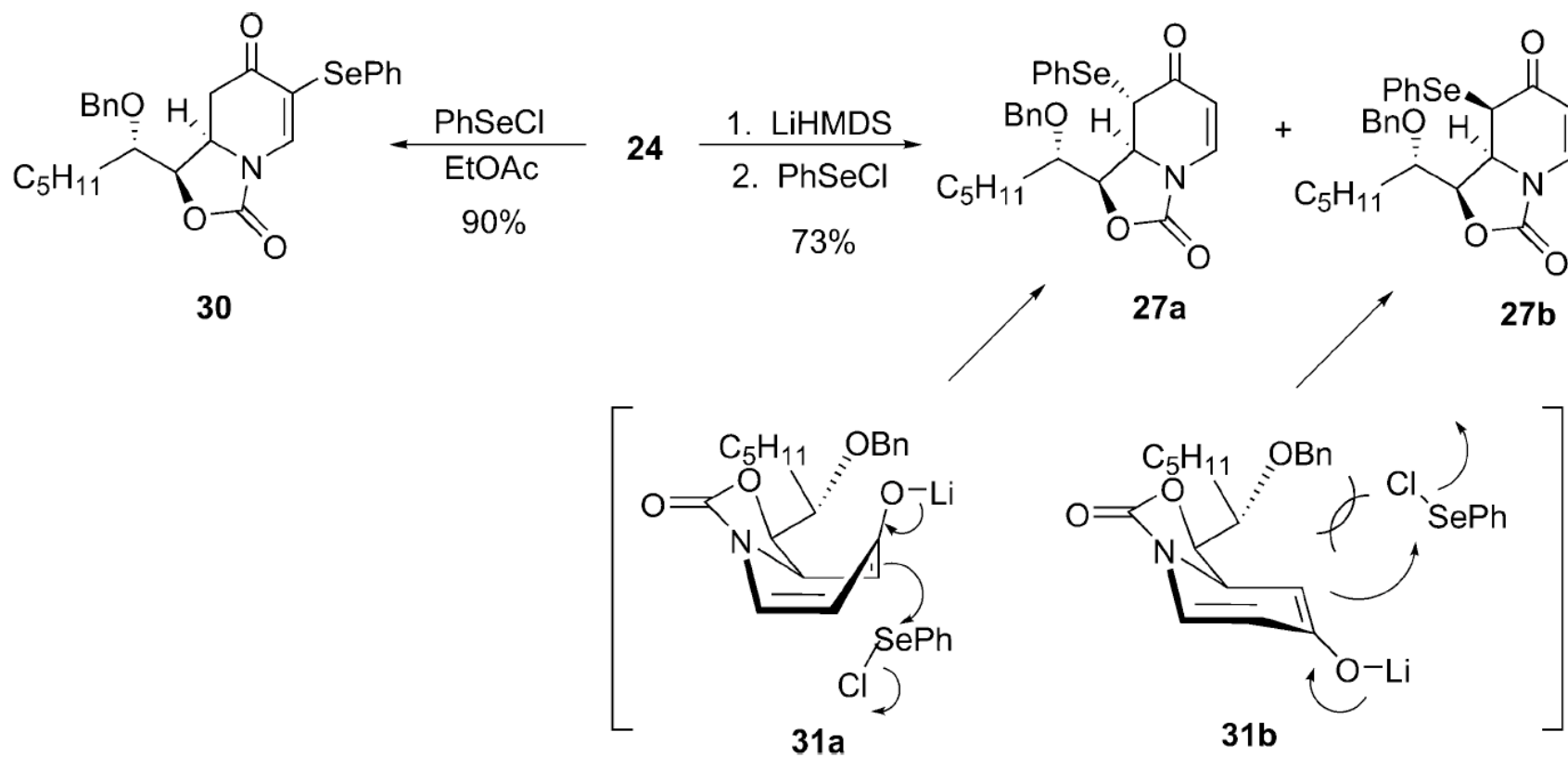
Protection steps to Intermediate 24



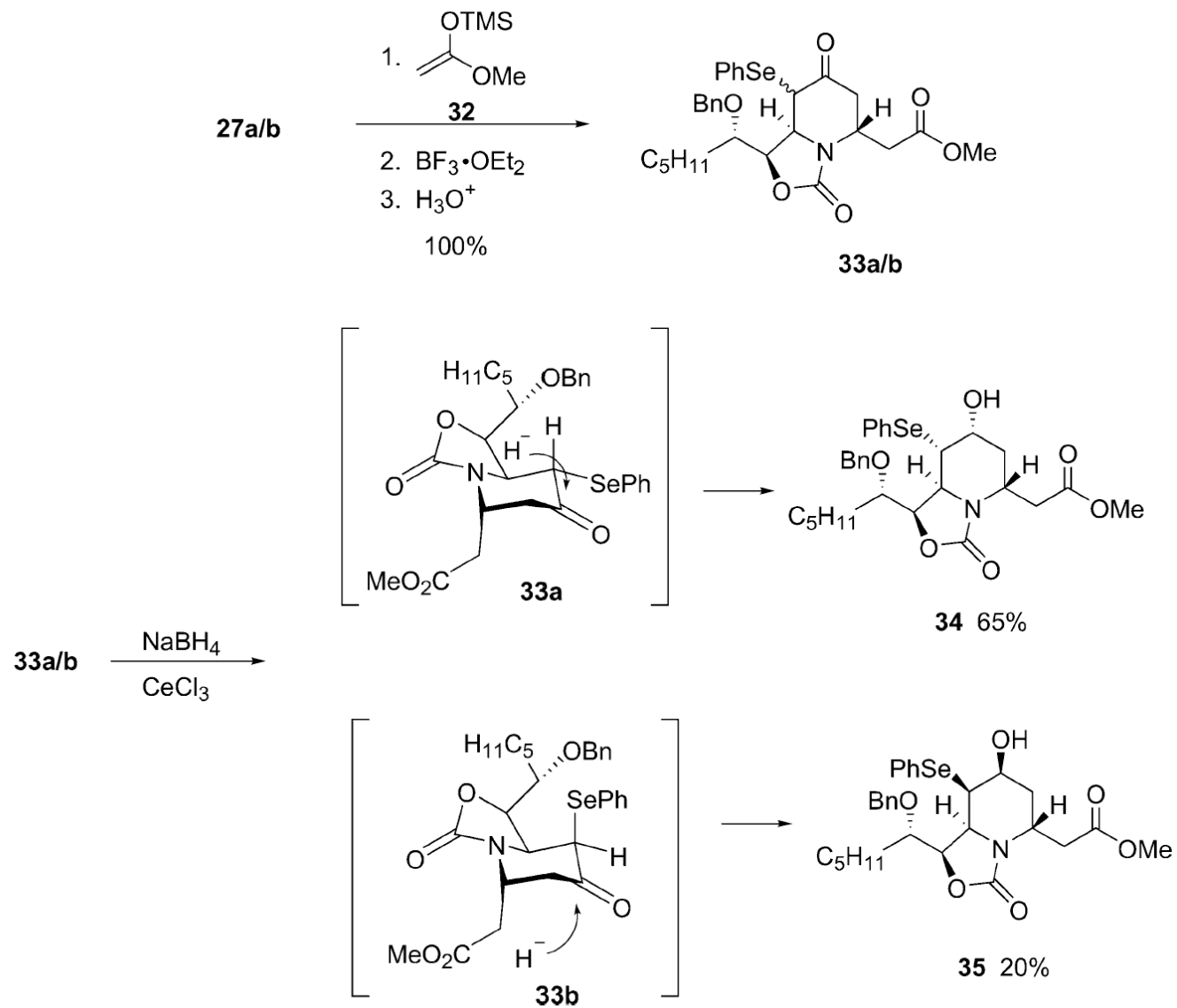
1,4-Addition and Reduction of Ketone



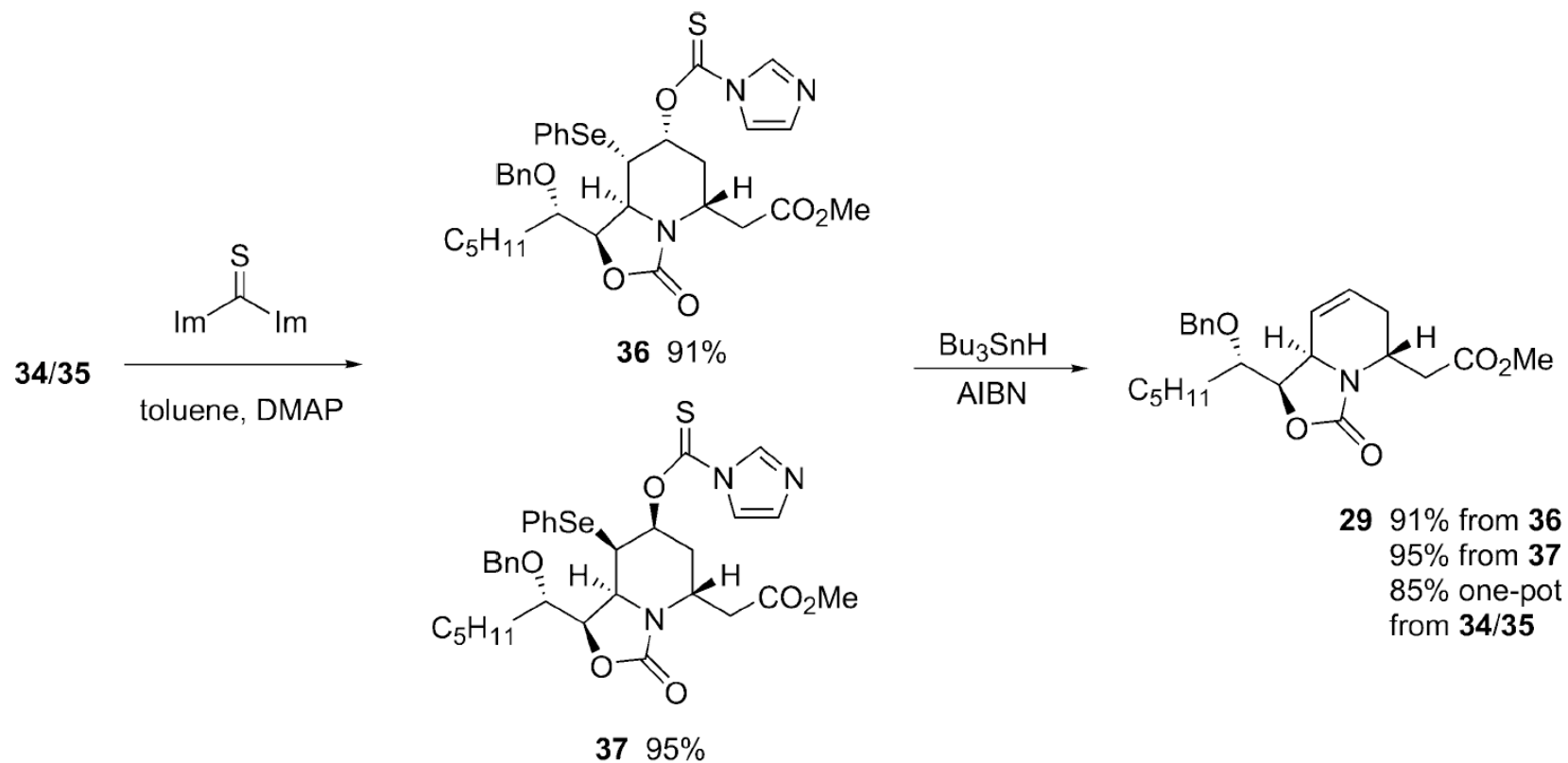
Selenation of Carbamate **24**



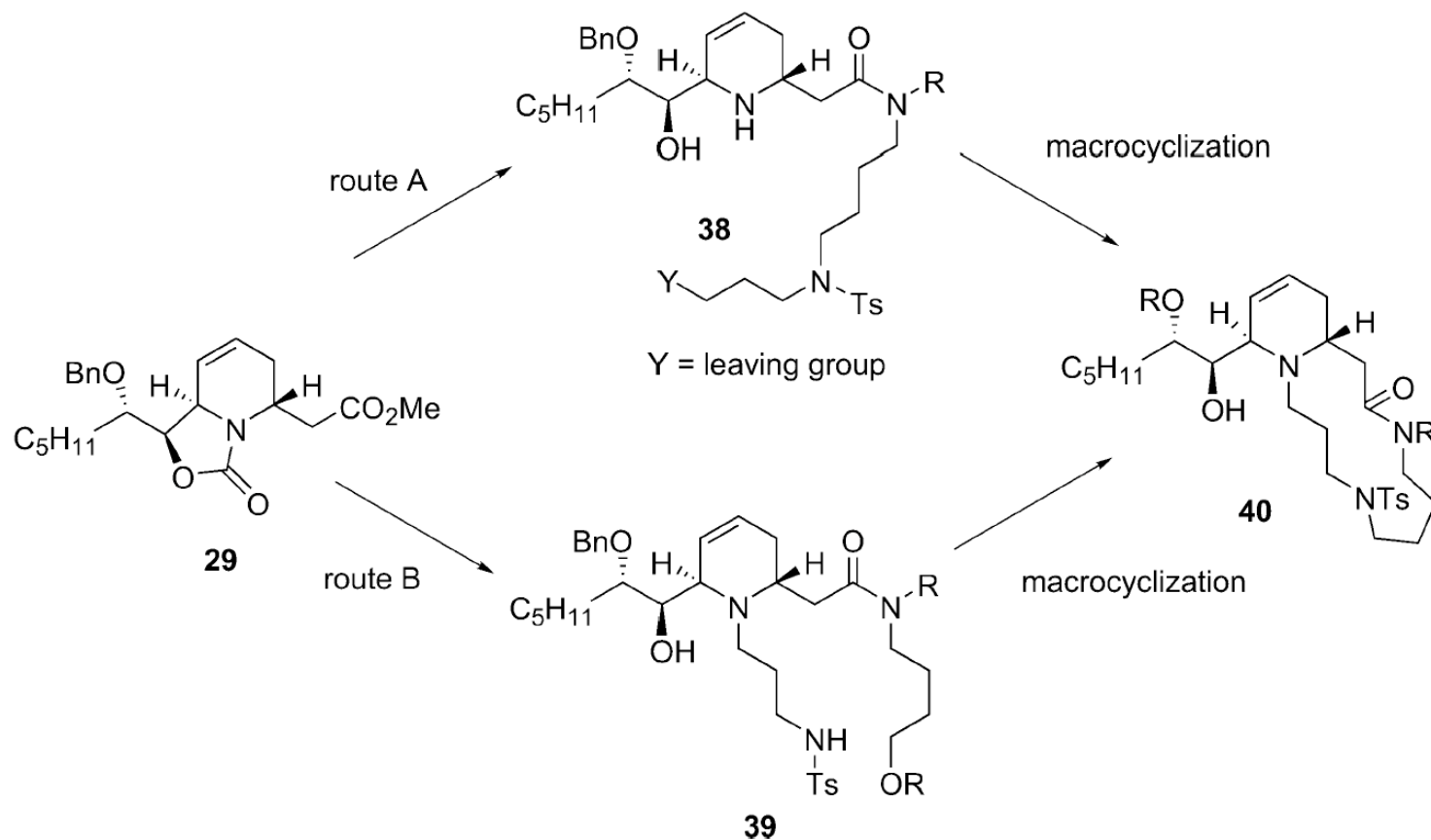
Stereoselective Addition of the Acetic Ester Unit



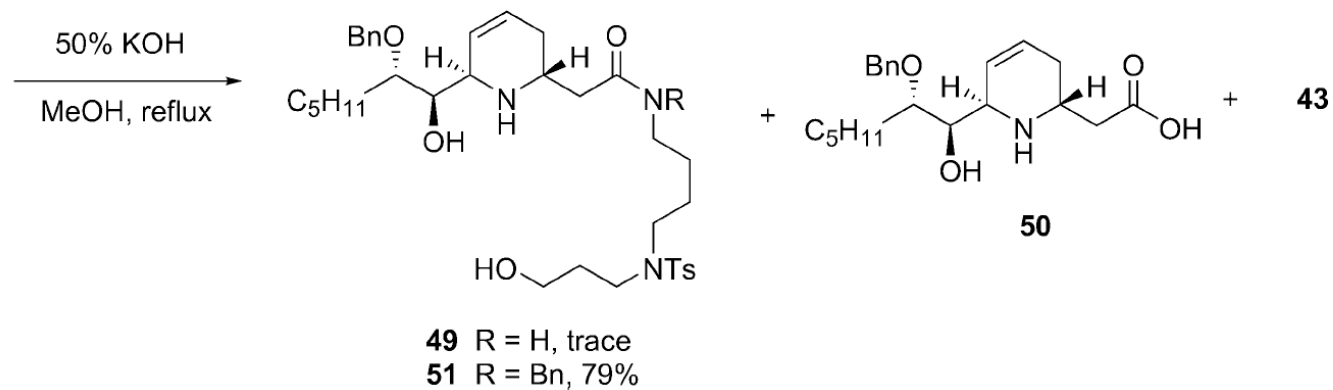
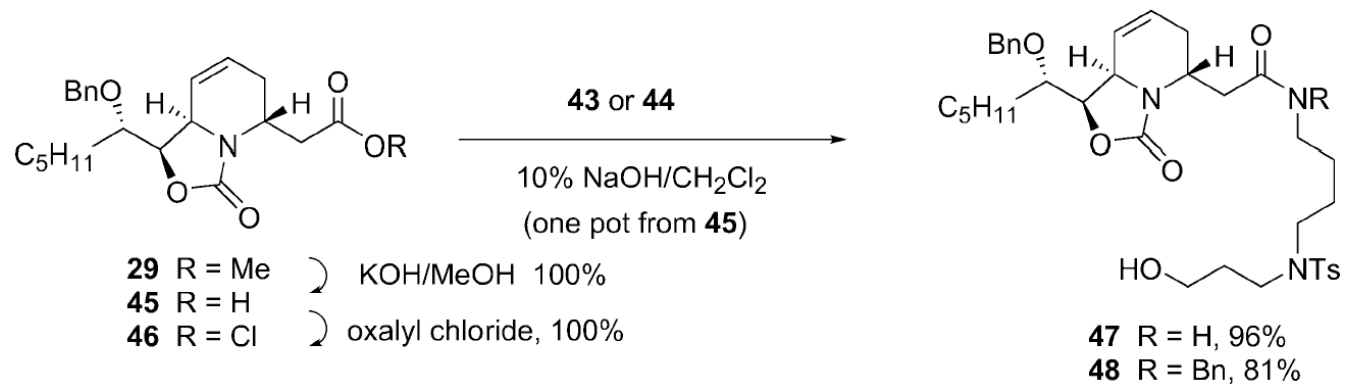
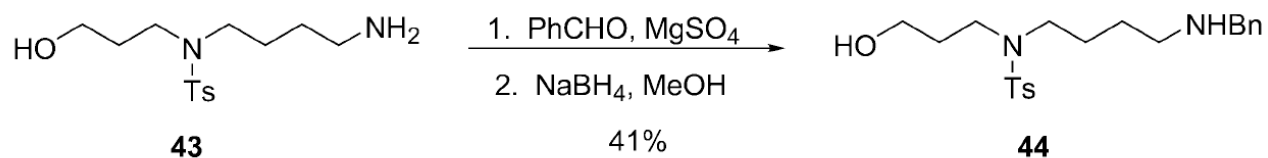
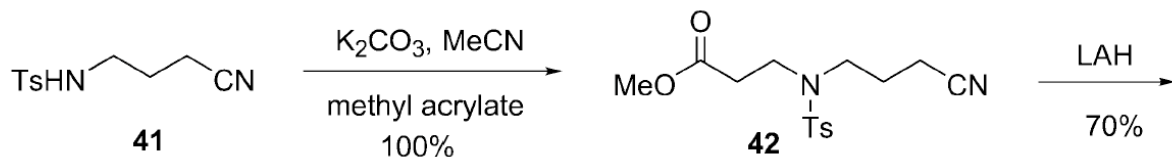
Elimination of *cis*-Beta-Hydroxyselenides **34** and **35**



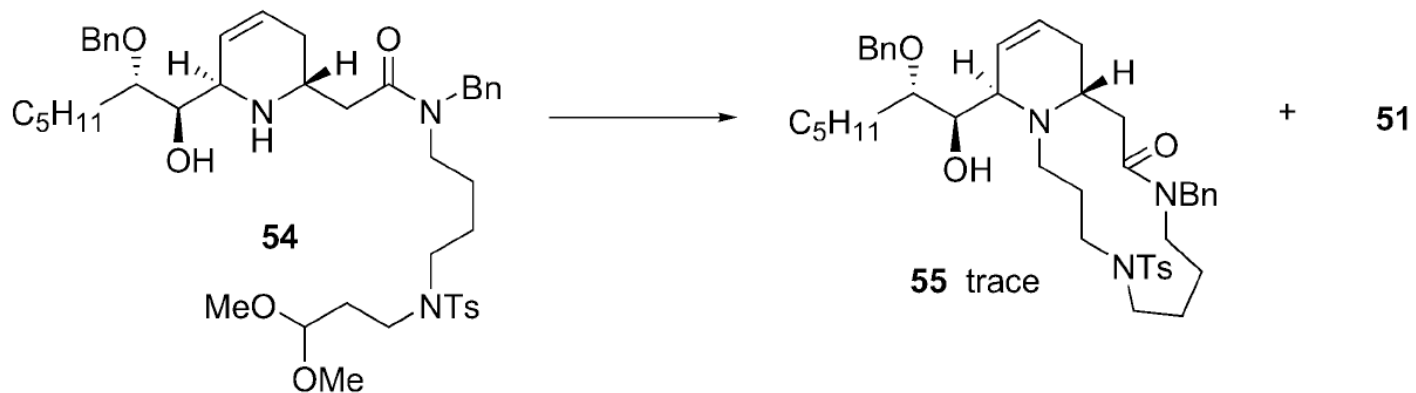
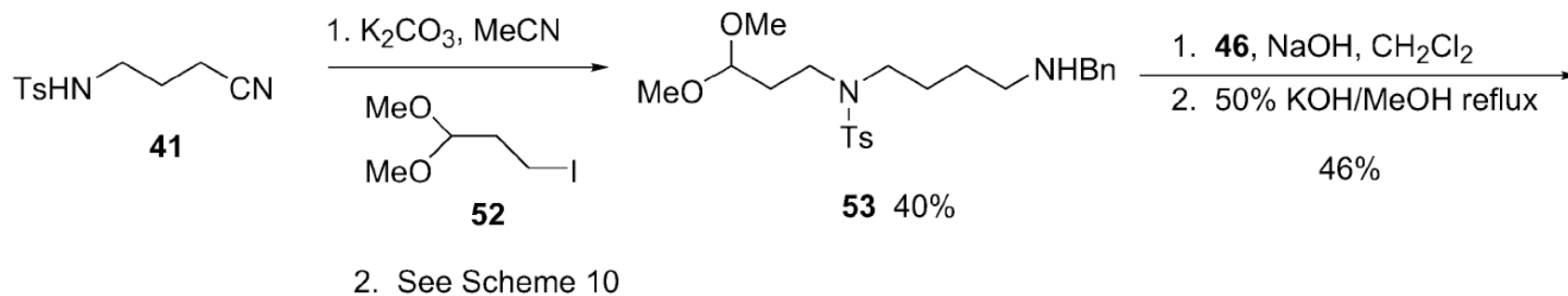
Synthetic Approaches to Macrocyclization and Completion of (+)-Cannabisativine



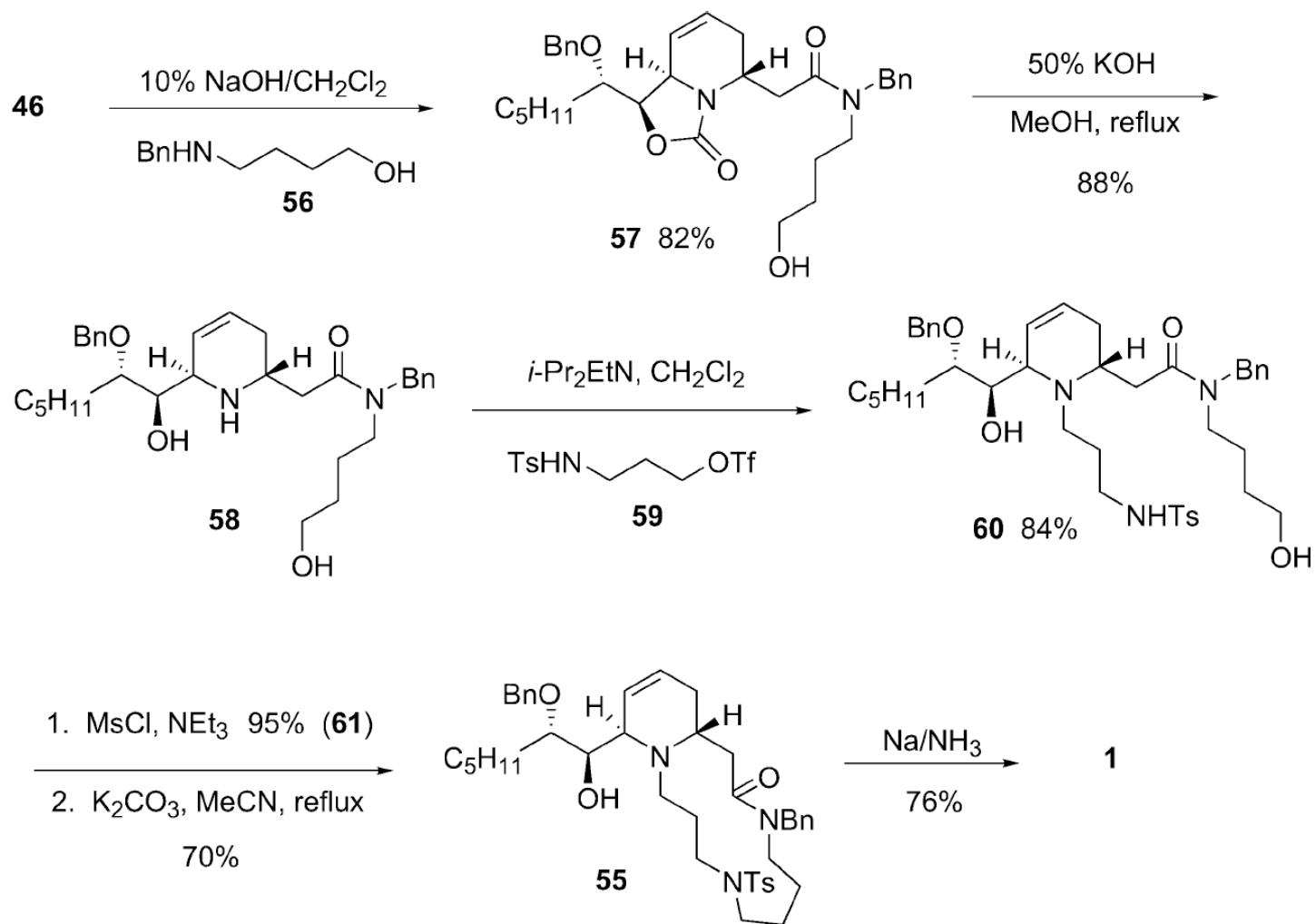
Route A Macrocyclization



Reductive Cyclization of **54** Attempted



Completion of Asymmetric Total Synthesis via Route B



Conclusions

- The first asymmetric synthesis of (+)-Cannabisativine (**1**) was accomplished in 19 steps with a high degree of stereocontrol.
- The key steps include: the successful metallo enolate addition to the chiral 1-acylpyridinium salt (**10**);
- Conversion of the dihydropyridone (**17**) to bicyclic carbamate (**24**);
- A diastereoselective Mukaiyama-Michael addition of an acetic acid unit;
- And a regioselective ketone to alkene conversion via the *cis*-beta-hydroxyxelenides (**34**) and (**35**).