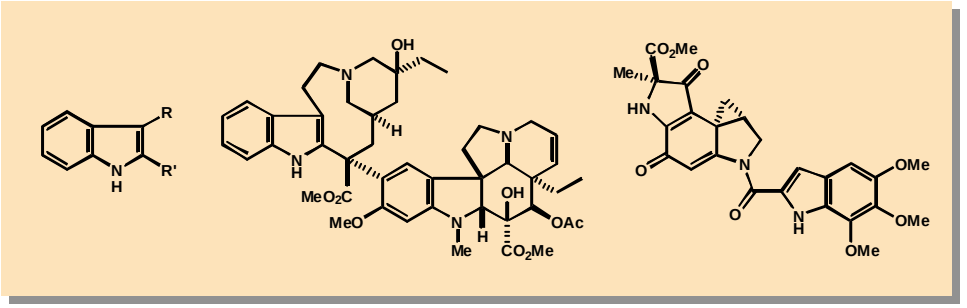
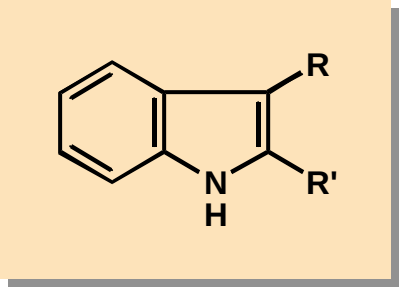
Indole Synthesis and Beyond



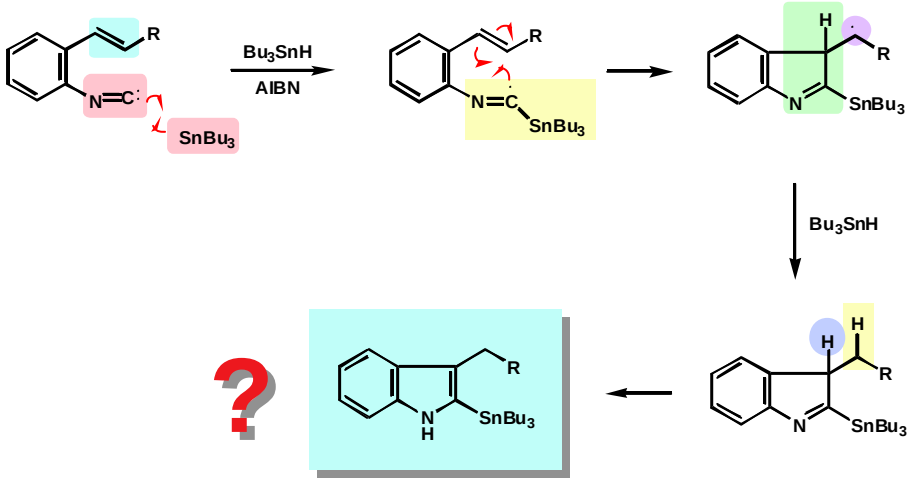
Tohru Fukuyama
Graduate School of Pharmaceutical Sciences
University of Tokyo

Development of New Indole Synthesis
- First-Generation -

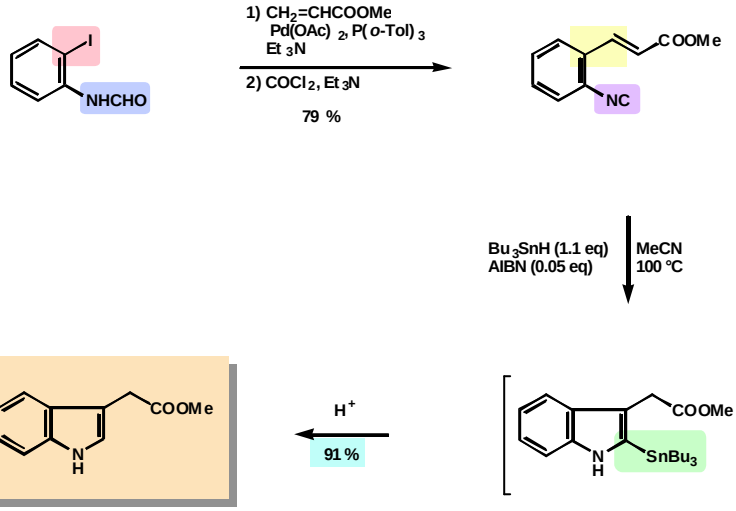


J. Am. Chem. Soc. **1994**, *116*, 3127.

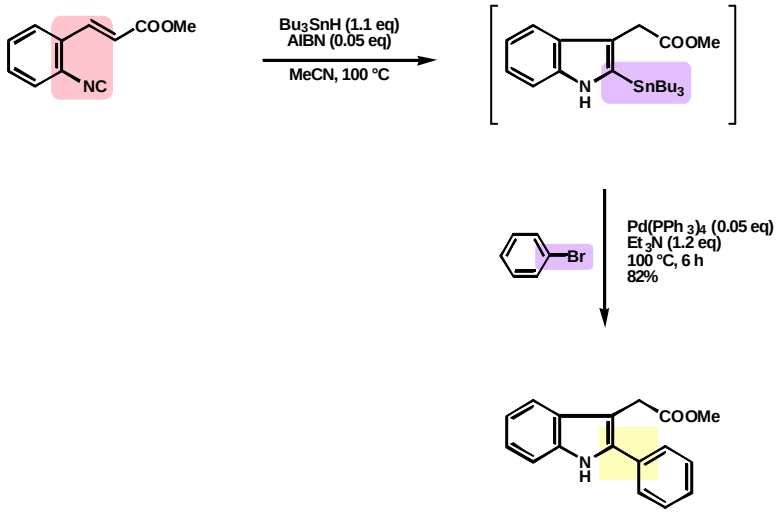
It all started with this idea at Rice Univ…



The idea worked!

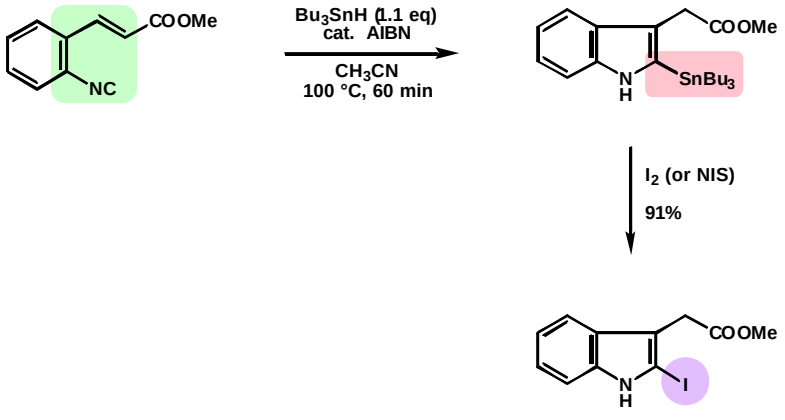


One-Pot Synthesis of 2,3-Disubstituted Indoles

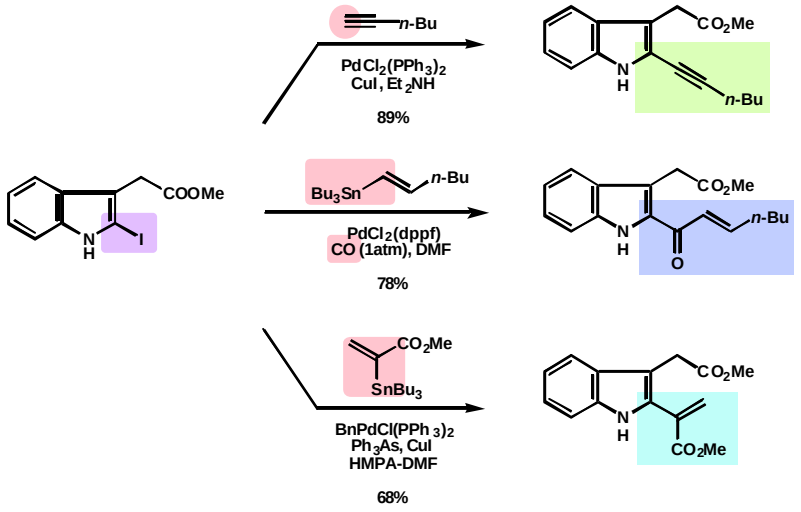


JACS, 116, 3127 (1994)

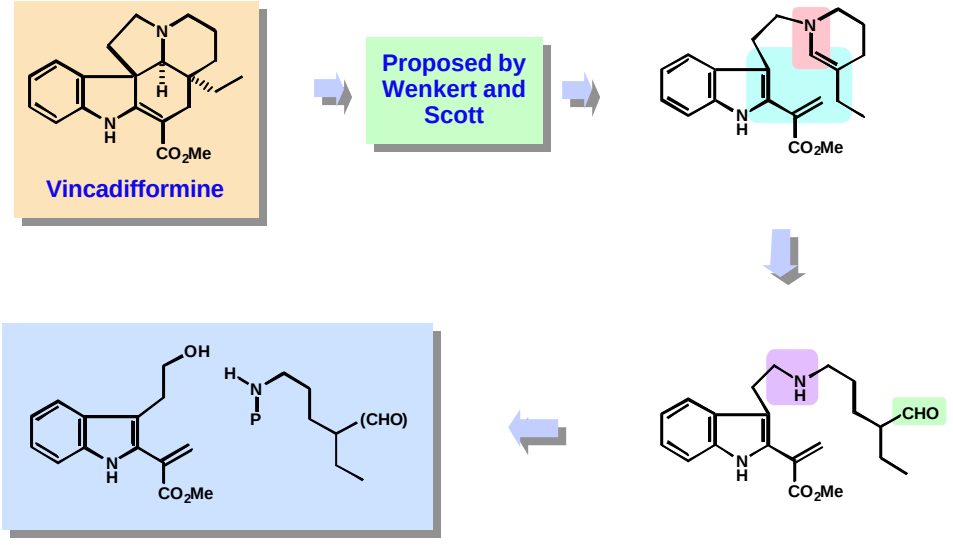
Synthesis of 2-Iodoindoles



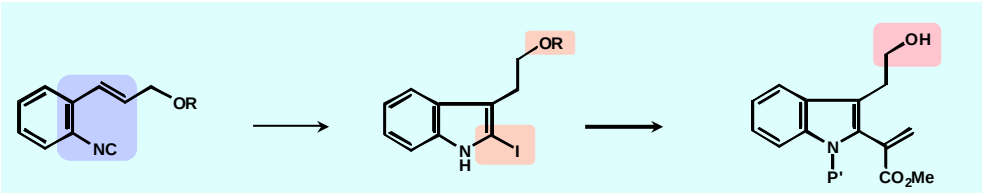
Versatility of 2-Iodoindoles

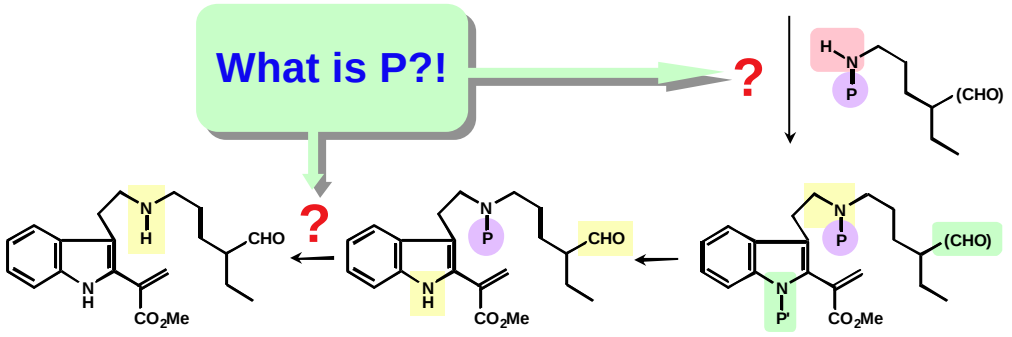


Application to Total Synthesis of Indole Alkaloids

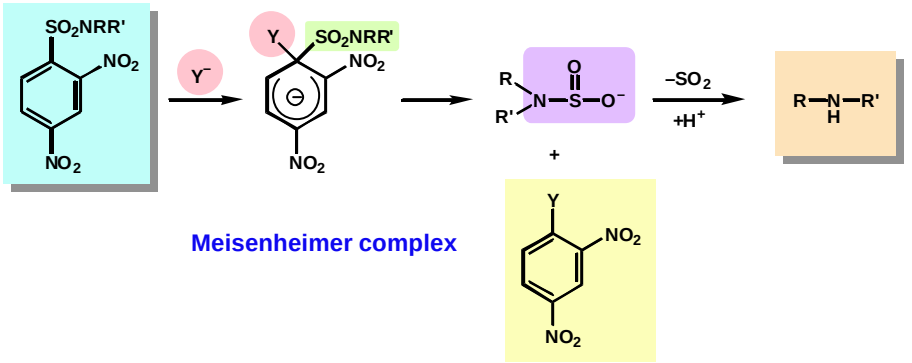


Problems to be Solved for Biomimetic Synthesis





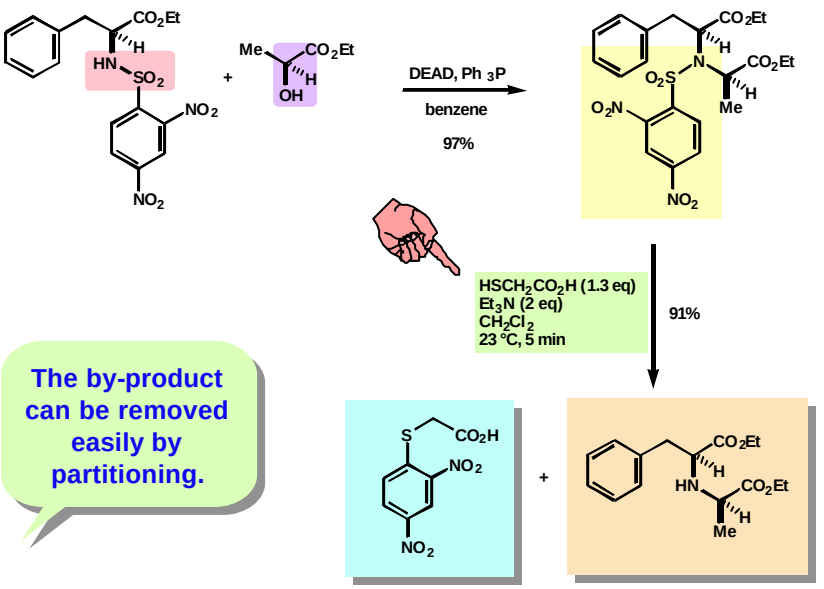
Found an Answer!

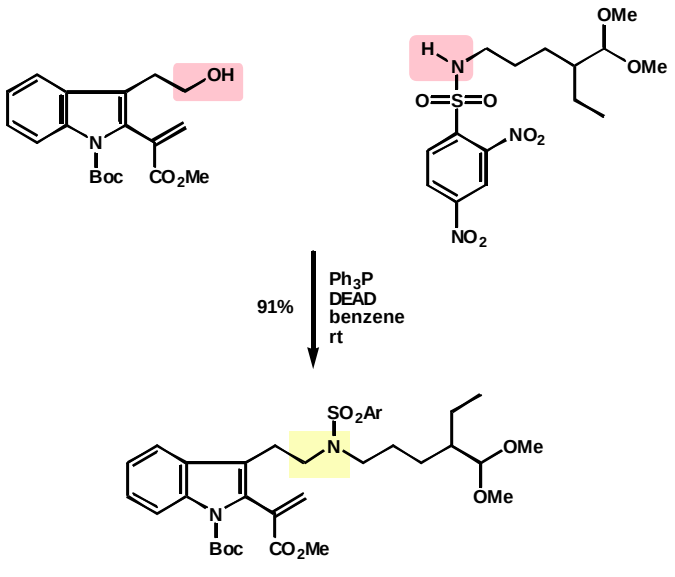


Meisenheimer complex

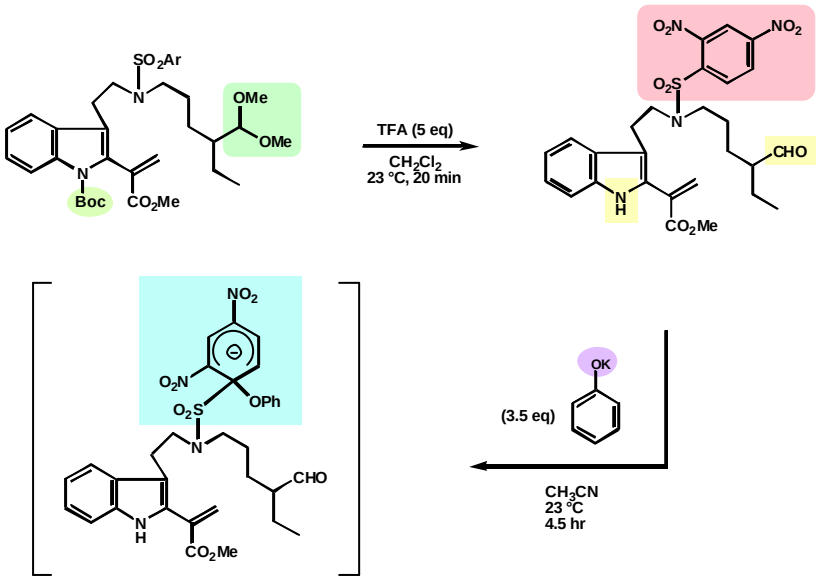
TL, 36, 6373 (1995)
TL, 38, 5831 (1997)

Mitsunobu reaction works particularly well.

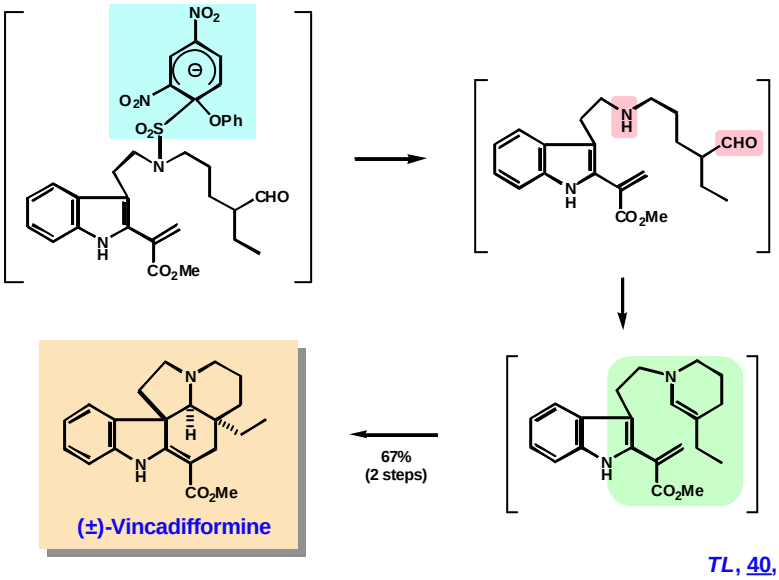




Removal of the Activating Group …

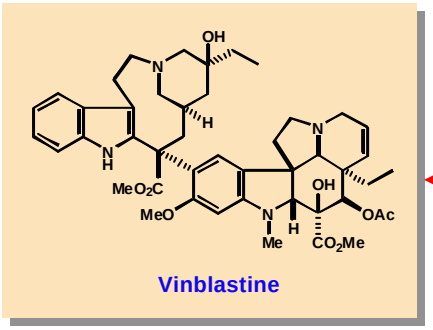


… Resulted in the Completion of the Synthesis



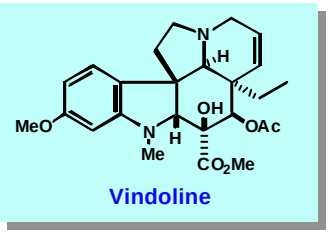
TL, 40, 1519 (1999)

Vindoline and Catharanthine

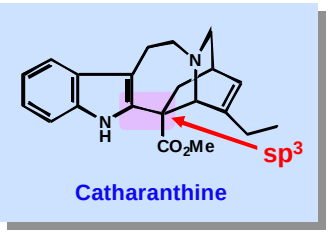


Vinblastine

Potier & Langlois

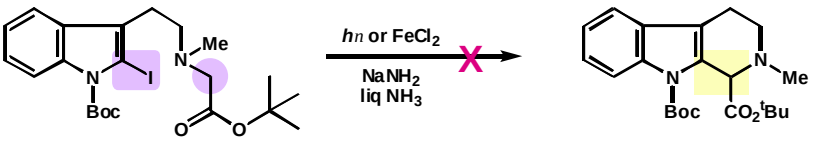


Vindoline

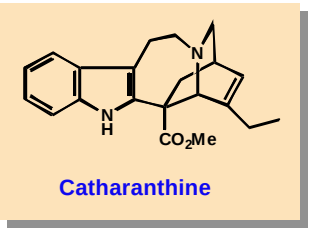


Catharanthine

Attempts to introduce an sp^3 carbon to the 2-position failed!

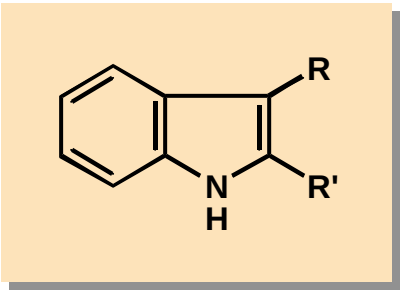


An entirely new indole synthesis needs to be developed for catharanthine!



Catharanthine

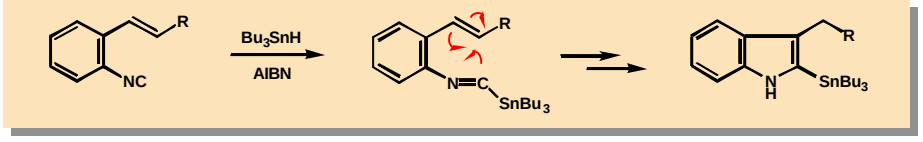
Development of New Indole Synthesis
- Second-Generation -



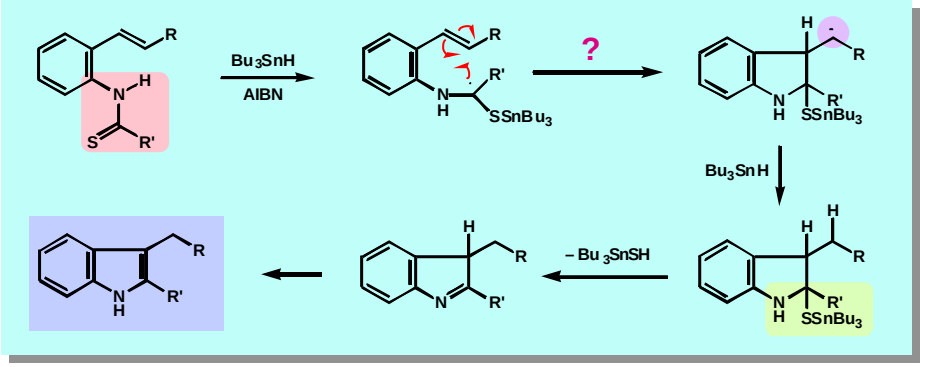
J. Am. Chem. Soc. **1999**, *121*, 3791.

How about this idea?

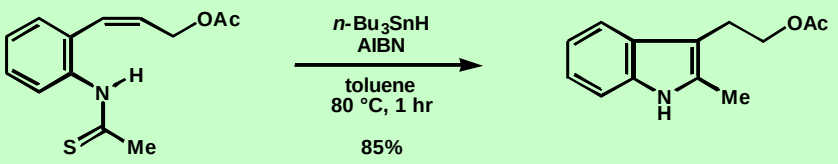
First-Generation



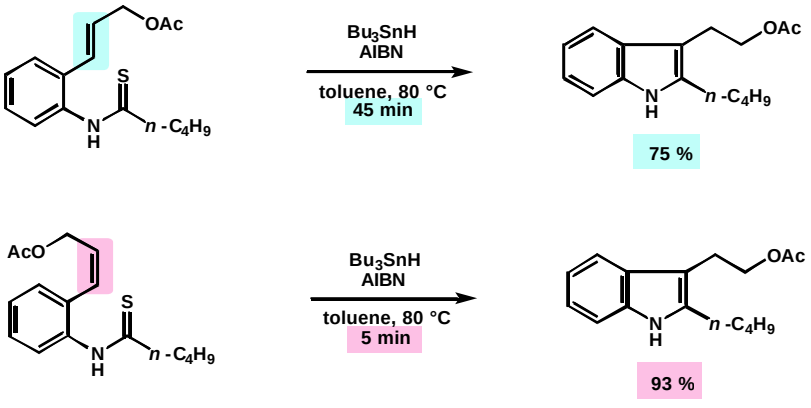
Second-Generation



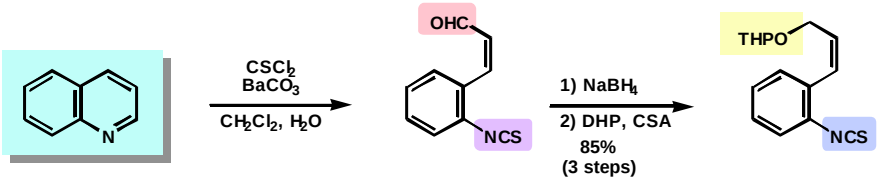
It worked !!!



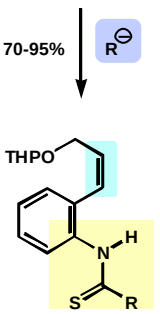
cis-Olefins are Better Substrates!

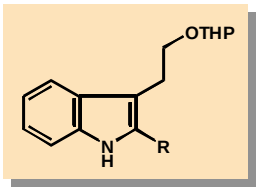


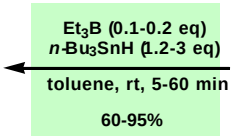
Conversion of Quinolines to Indoles !!



Hull, *J. Chem. Soc., Perkin I*, 922 (1975)

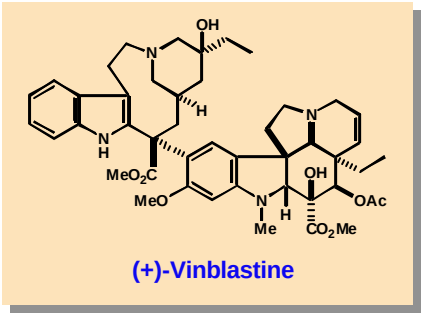




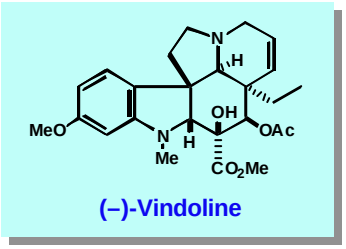


JACS, 121, 3791 (1999)

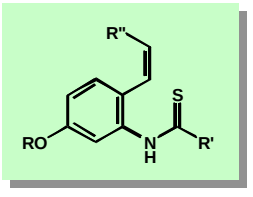
Total Synthesis of (+)-Vinblastine via (–)-Vindoline



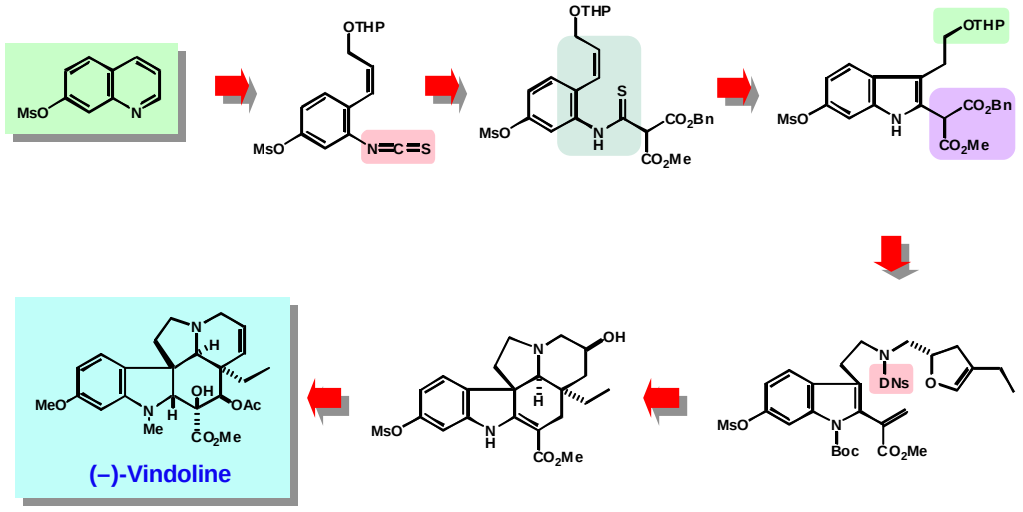
(+)-Vinblastine

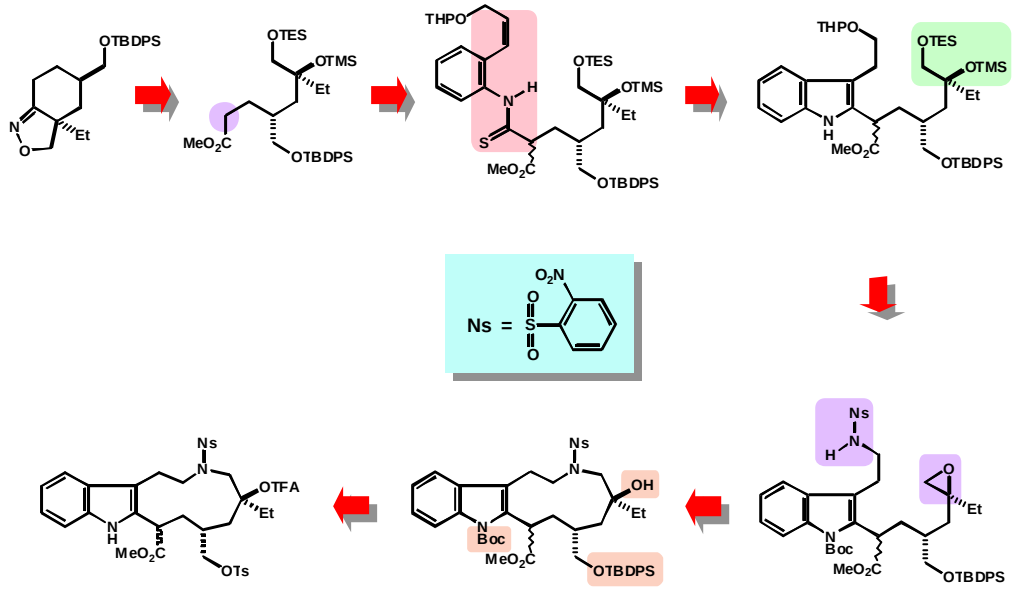


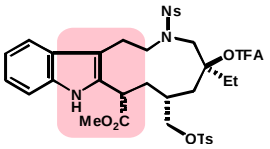
(–)-Vindoline

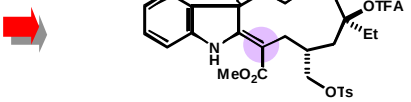


Total Synthesis of (+)-Vinblastine *via* (–)-Vindoline

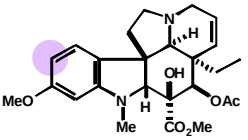


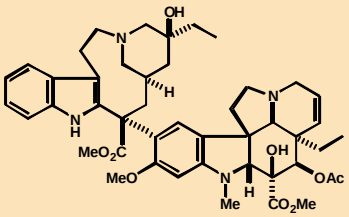




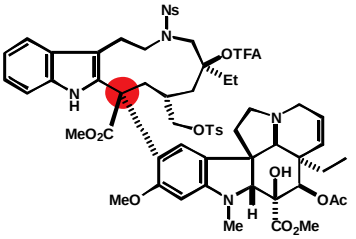


97% !



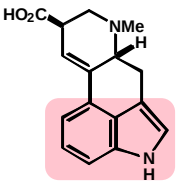


(+)-Vinblastine

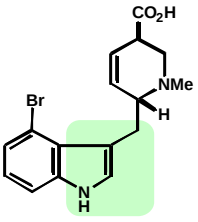


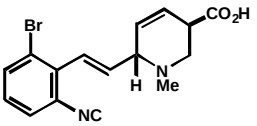
J. Am. Chem. Soc. **2002**, *124*, 2137.

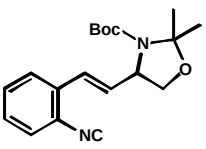
Synthetic Approaches to (+)-Lysergic Acid

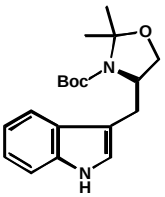


(+)-Lysergic acid



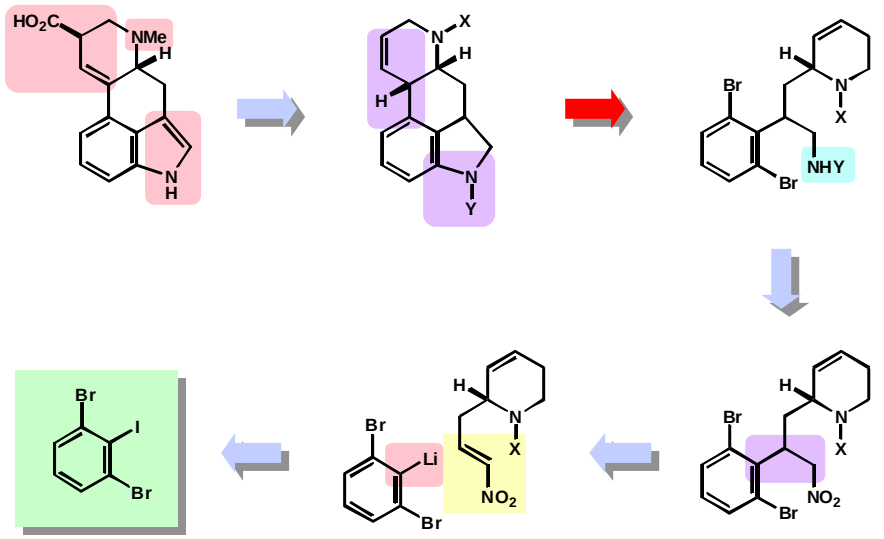




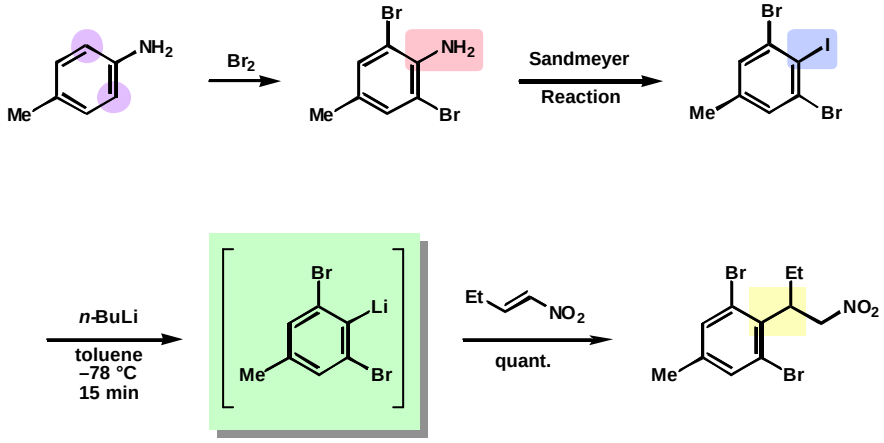


Luckily(?!), our first-generation indole synthesis did not work!

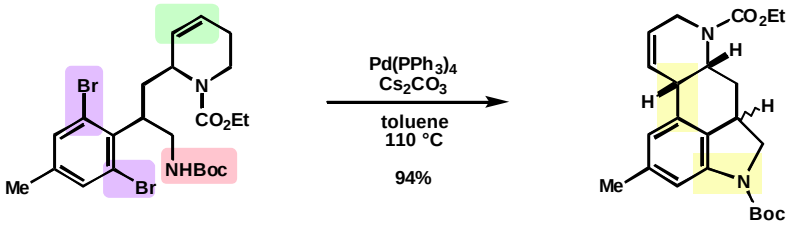
A One-Pot Heck-Buchwald Reaction?!

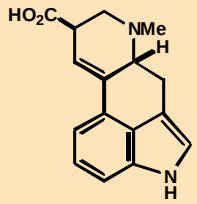


Since our methodology did not work, we were compelled to explore the other possibilities that eventually brought us a great success!



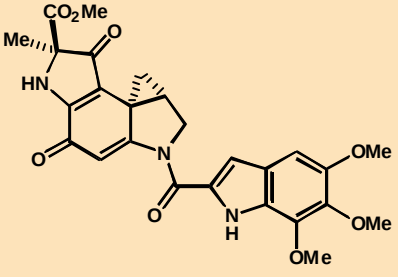
Model Studies on Lysergic Acid Synthesis





(+)-Lysergic acid

Total Synthesis of (+)-Duocarmycin A



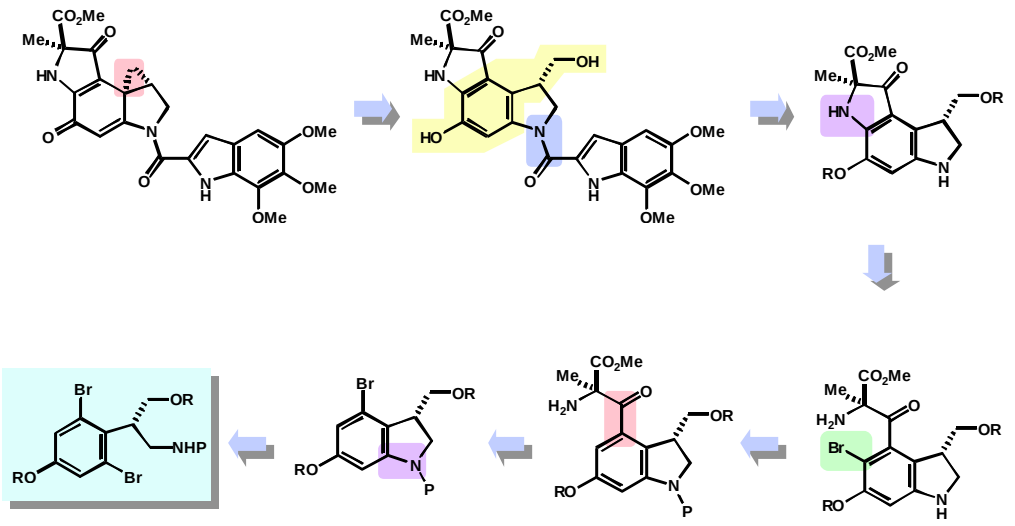
Isolation: Nakano *et al., J. Antibiot.,* 41, 1915 (1988)

Structure Determination: Sano *et al., Chem. Pharm Bull.*, 36, 3728 (1988)

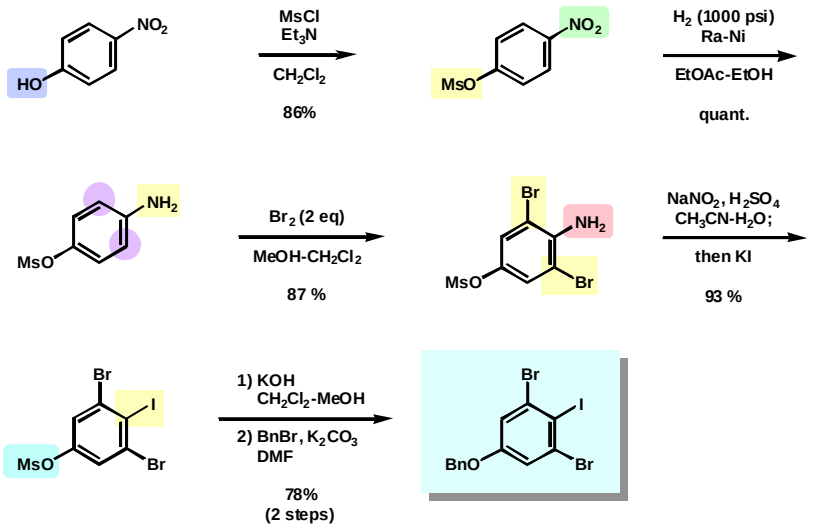
Total Syntheses: Terashima *et al., Tetrahedron Lett.*, 31, 6699 (1990)

Boger *et al., J. Am. Chem. Soc.*, 118, 2301 (1996)

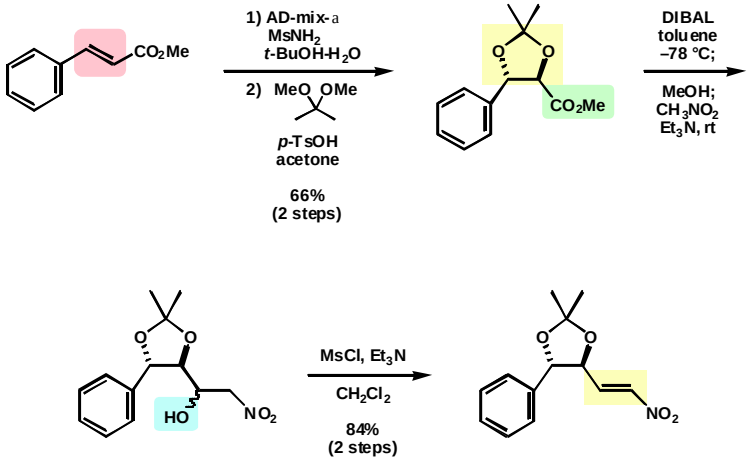
Retrosynthetic Analysis



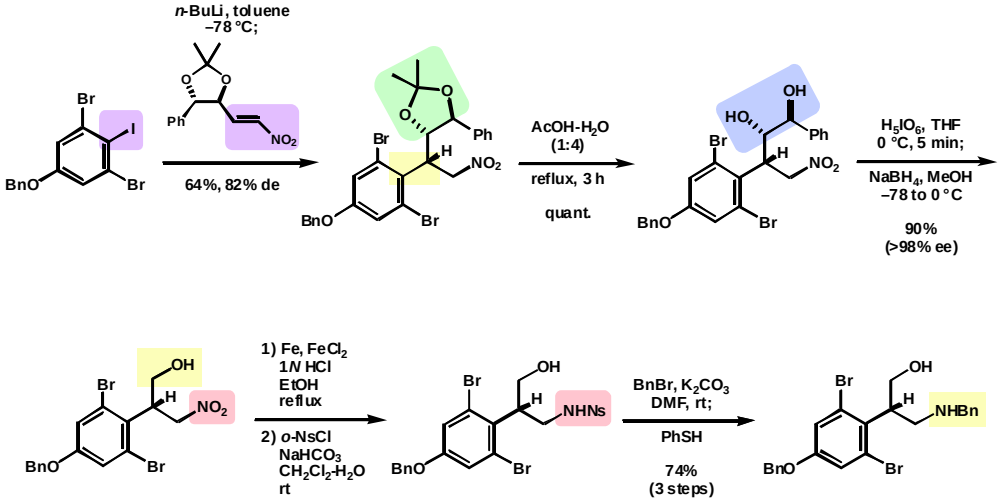
Preparation of *o,o'*-Dibromoiodobenzene



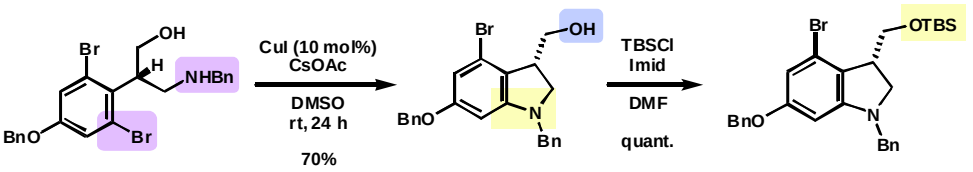
Preparation of the Chiral Nitroalkene

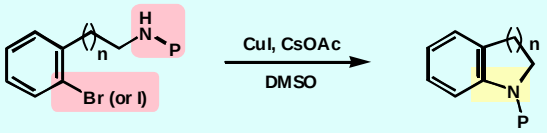


Diastereoselective Addition to Nitroalkene



Novel Cu-Mediated Aryl Amination!!

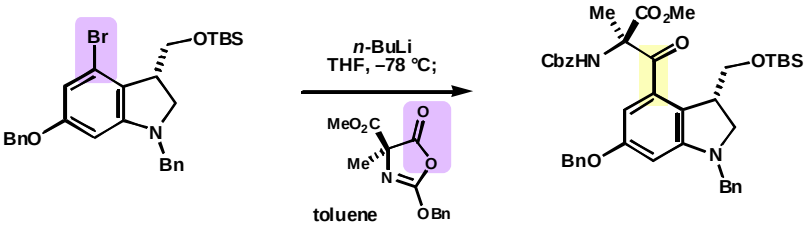


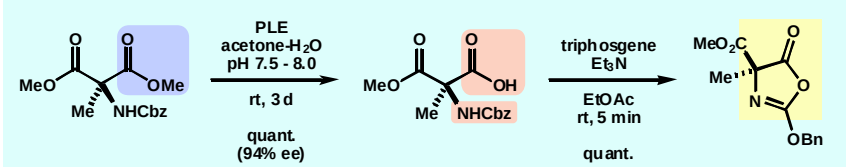


P = H, Bn, Ns, Ac, Cbz, Alloc, Boc
n = 1-3

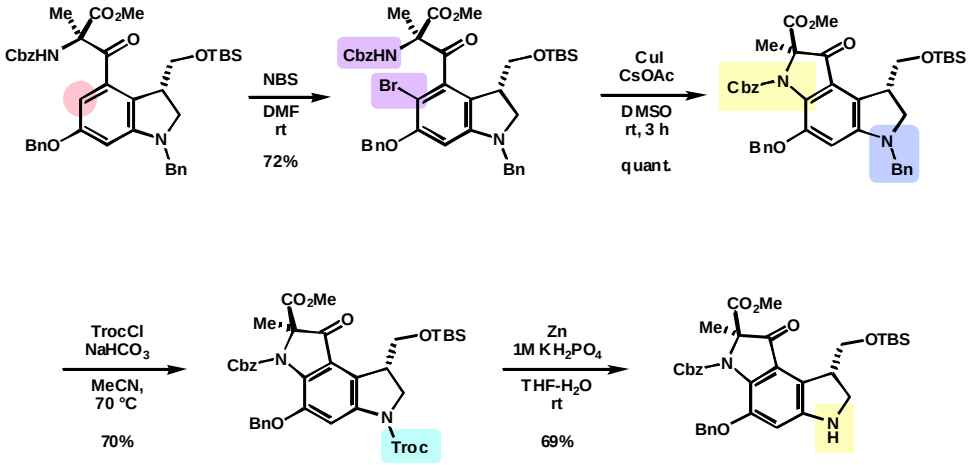
Synlett 231 (2002)

Addition to Optically Active Azlactone

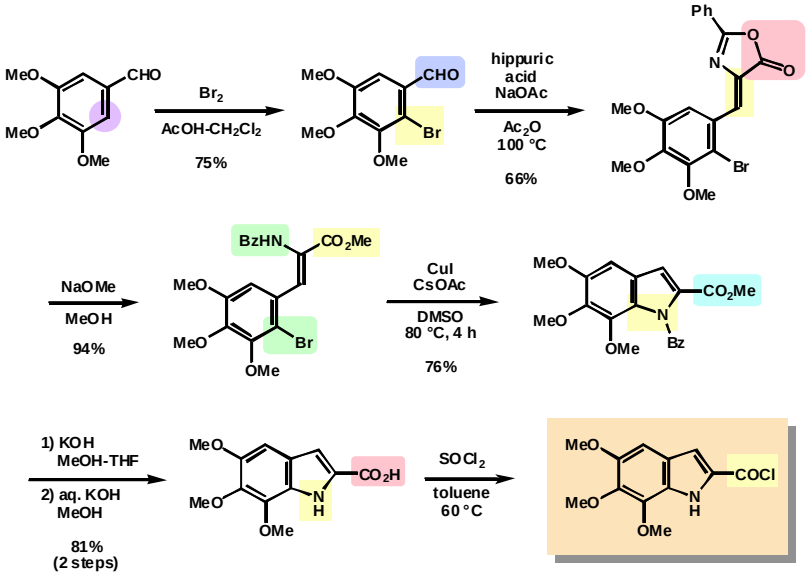




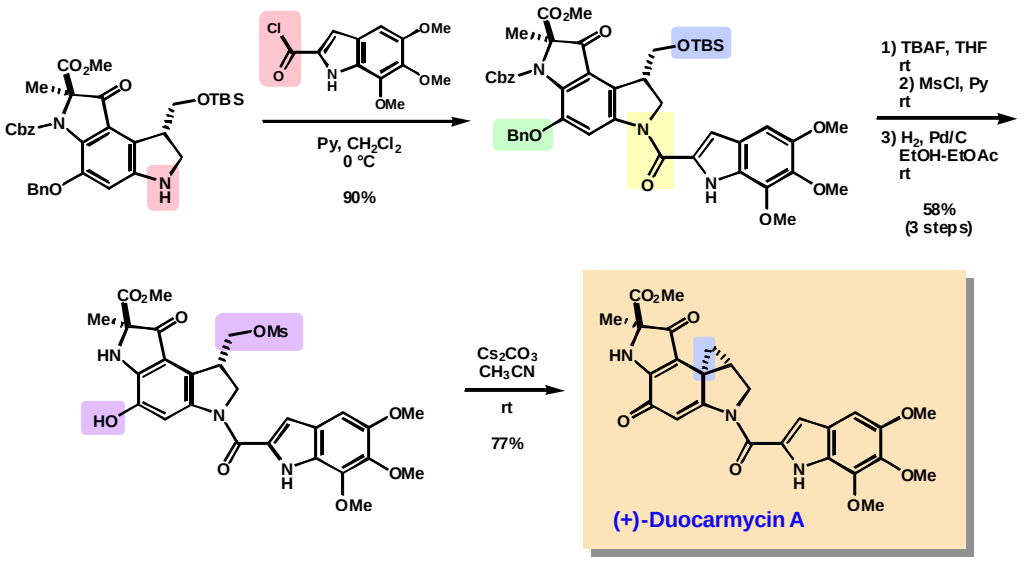
Construction of the Tricyclic Skeleton



Preparation of Indolecarboxylic Acid



Completion of the Total Synthesis



Fukuyama Group 2002