

Progress Towards the Total Synthesis of (+)-Nodulisporic Acid A

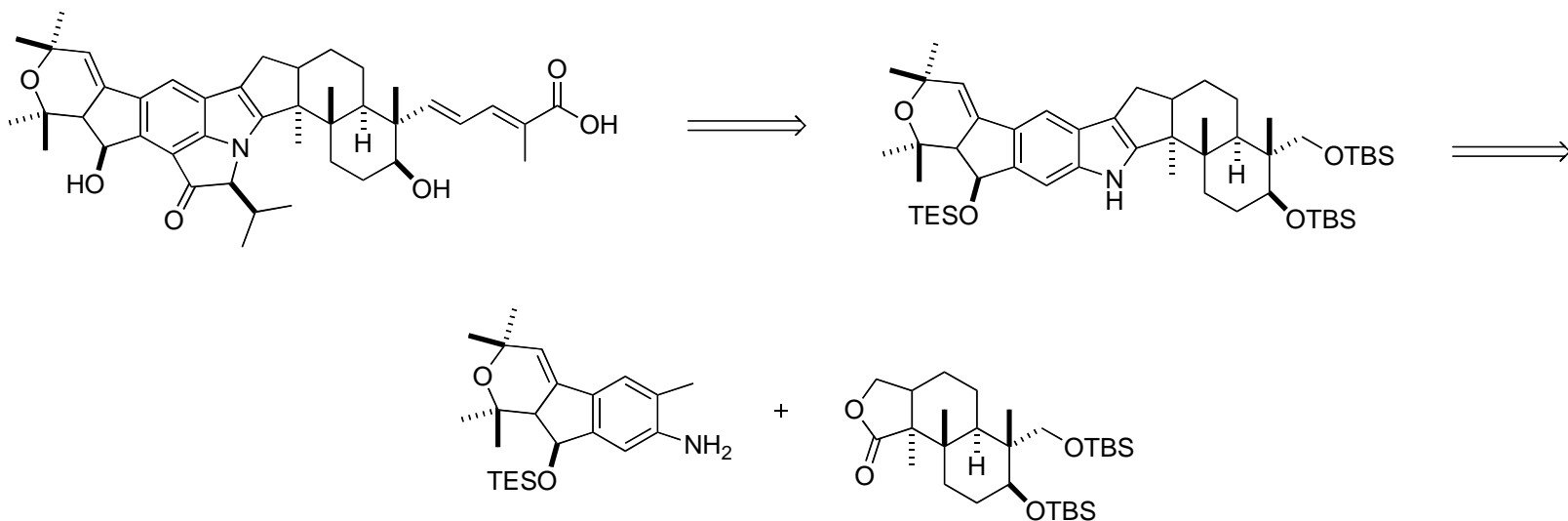
Amos B. Smith III, Akin H. Davulvu, Young Shin Cho,
Kazuyuki Ohmoto, Laszlo Kurti, and Haruaki Ishiyama

Mark Mans

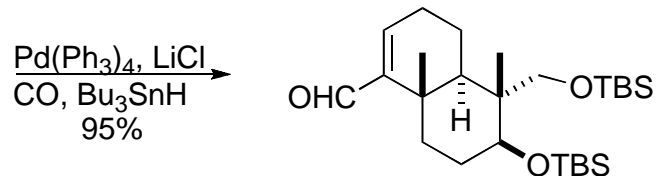
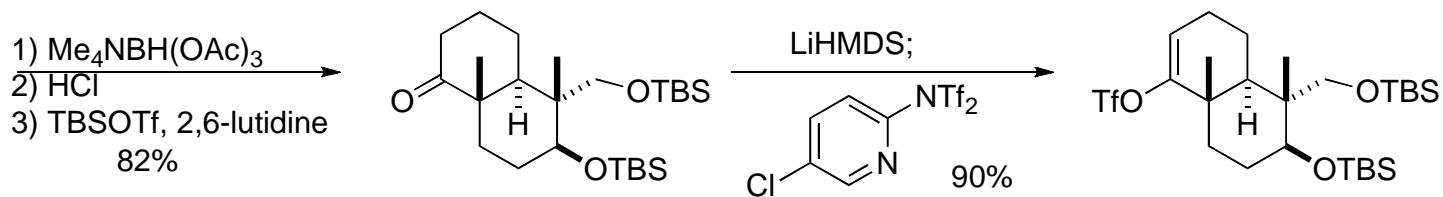
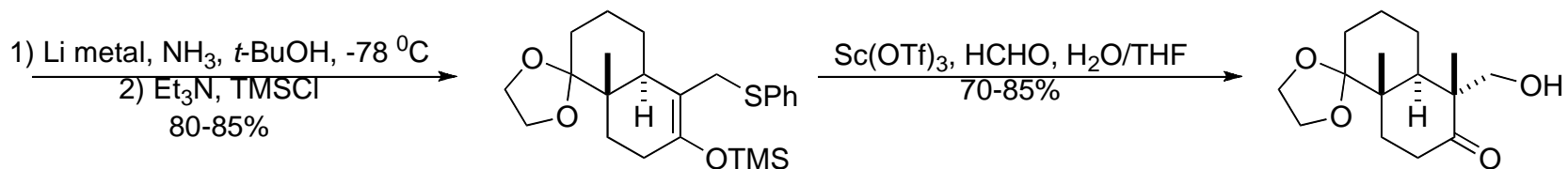
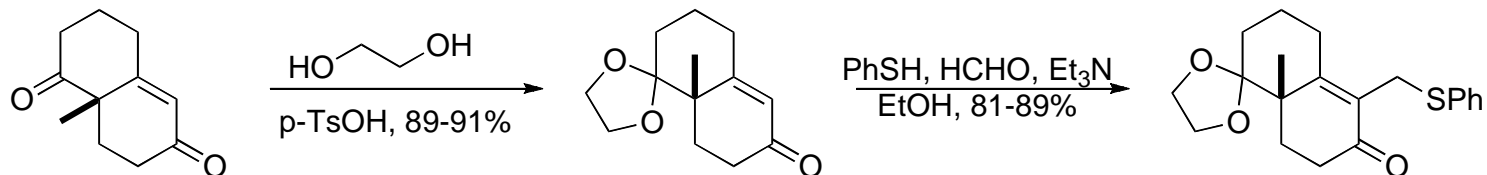
June 27, 2007

Isolation, Activity, and Retrosynthesis

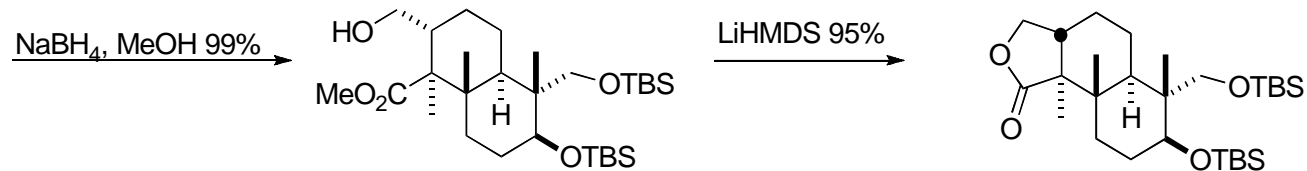
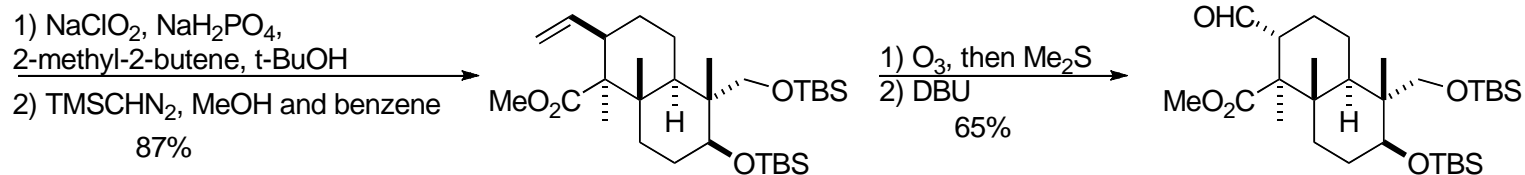
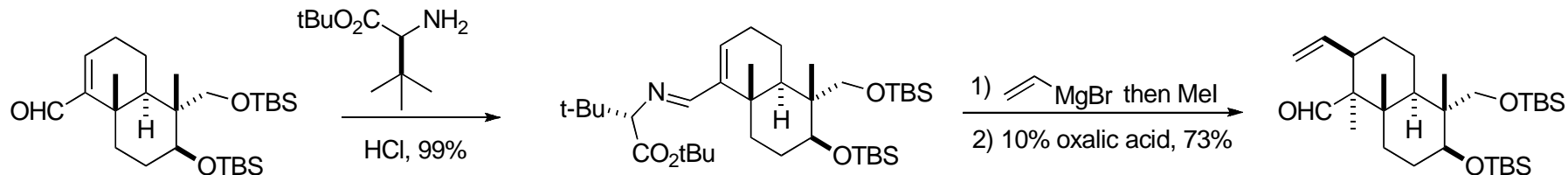
- Isolated in 1997 by Ondeyka and co-workers at Merck.
- Nodulisporic Acid A very effective against flea and tick infestations in dogs and cats (>10 times more effective than currently prescribed flea insecticides).
- Nodulisporic Acid A is active only against glutamate-gated ion channels specific to invertebrates, thus no apparent toxicity to the animal host.



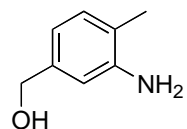
Synthesis of the Eastern Hemisphere



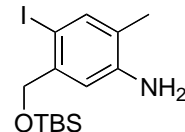
Synthesis of the Eastern Hemisphere



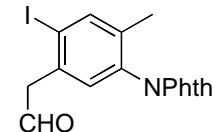
Work on the Western Hemisphere



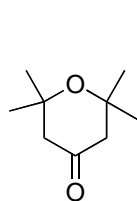
1) TBSCl, imidazole, DMF
2) $\text{BnNMe}_3\text{ICl}_2$, CaCO_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$

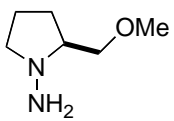


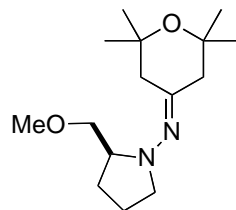
1) phthalic anhydride, Et_3N , toluene
2) HCl , THF
3) NaOCl , TEMPO, NaBr , NaHCO_3
 $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$



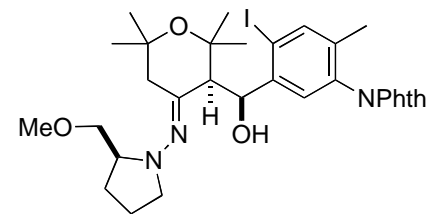
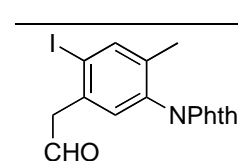
70% five steps




p-TsOH, 99%

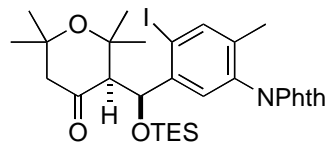


t-BuLi, THF, -78°C then

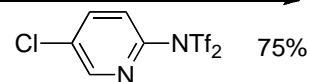


1) O_3 , CH_2Cl_2 -78°C
2) TESOTf, 2,6-lutidine, CH_2Cl_2

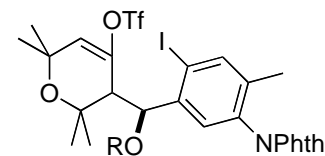
40% two steps



LiHMDS, THF, -78°C then



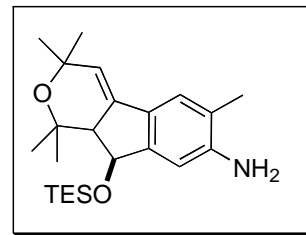
75%



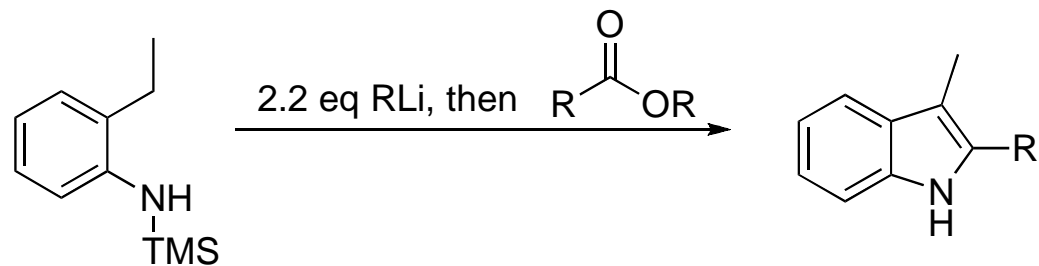
R = TES

1) $\text{Me}_3\text{SnSnBu}_3$, $\text{Pd}(\text{PPh}_3)_4$, Bu_4NBr , Li_2CO_3 , xylene
2) H_2NNH_2

59% two steps

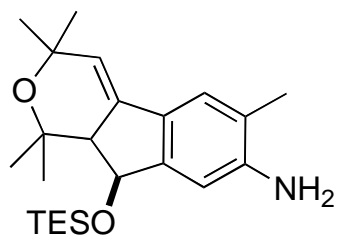


Attempted Coupling

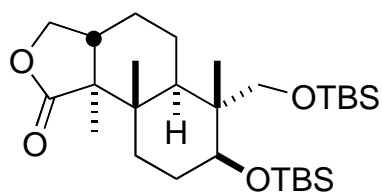


Developed in Smith Lab in 1980s

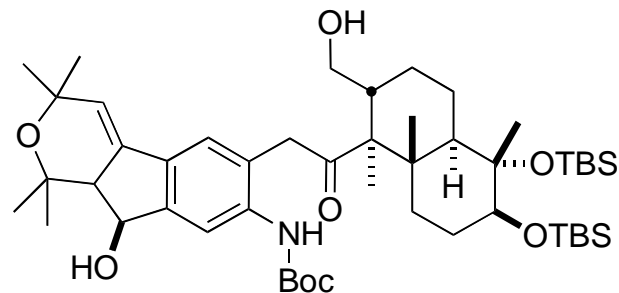
Indole Formation



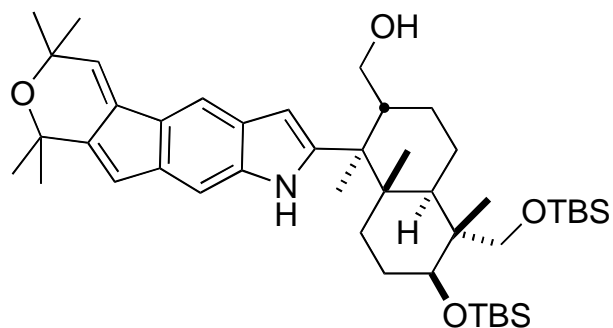
1) Boc₂O 86%
2) TBAF 94%
3) t-BuLi (3 eq) then



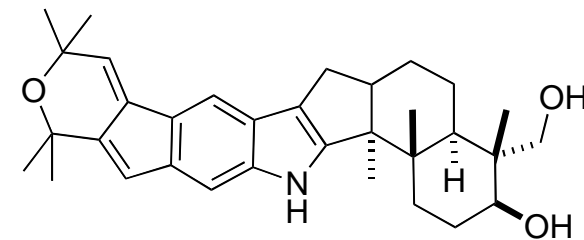
HMPA, 67%



TFA, CH₂Cl₂
loss of OH

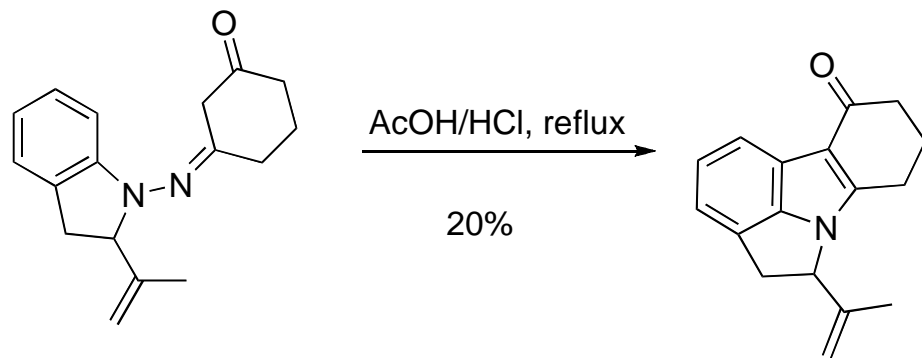
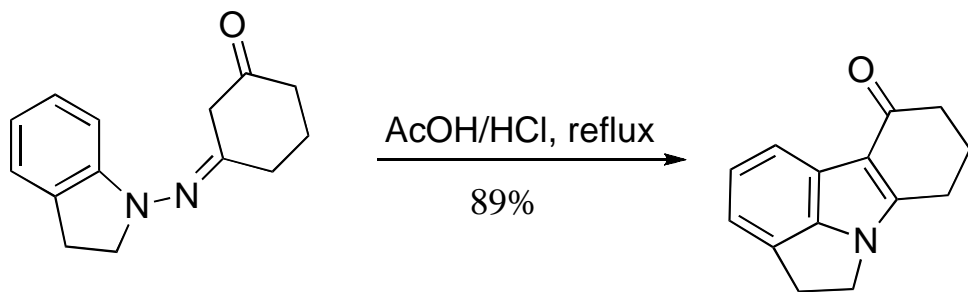
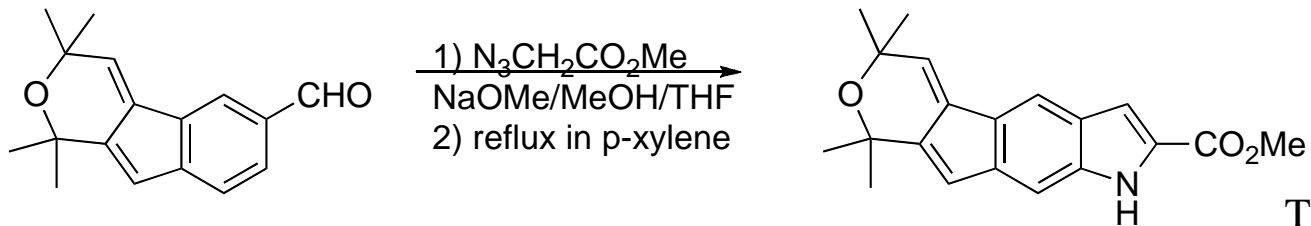


1) MsCl, DMAP, CH₂Cl₂, 93%
2) t-BuMgCl
3) TFA, CH₂Cl₂, 48% two steps

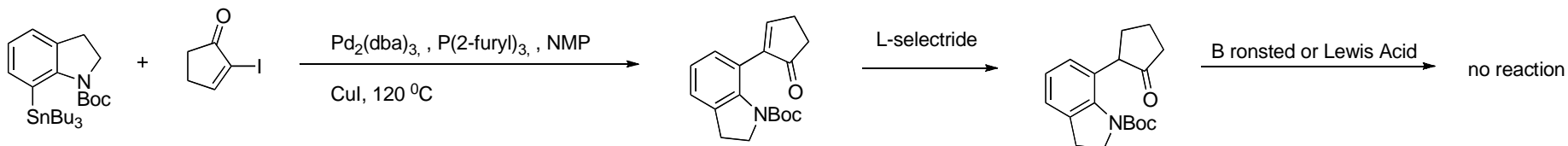
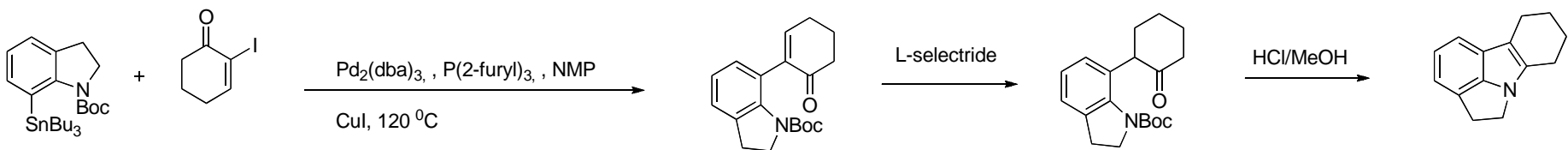


Heptacyclic core of Nodulisporic Acid A

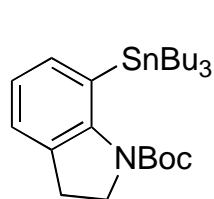
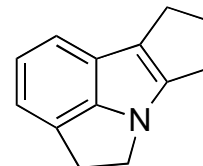
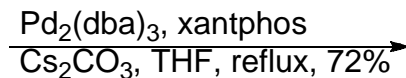
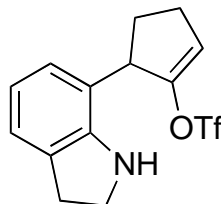
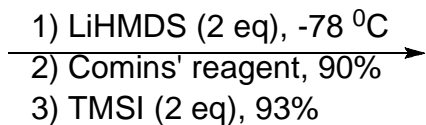
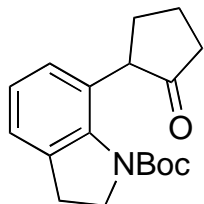
Alternative Indole Syntheses



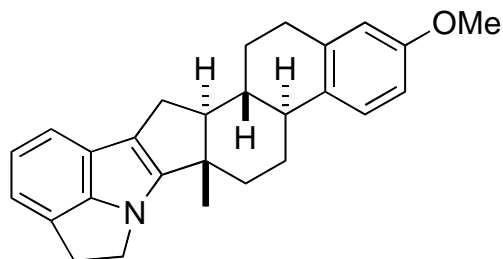
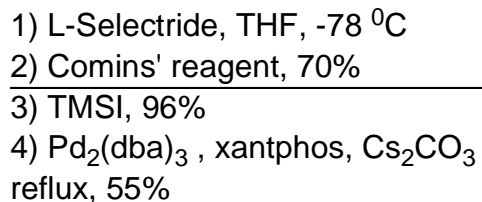
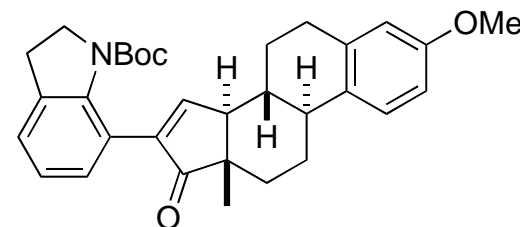
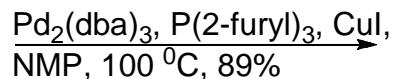
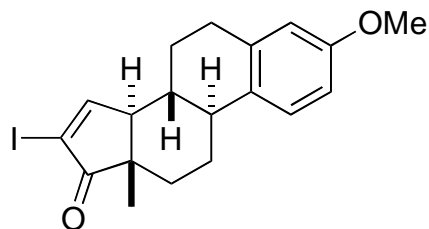
A Stille Cross-Coupling Approach



Preparation of Highly Strained Indole Core



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Conclusion

- Achieved the synthesis of the ABCEFGH heptacyclic core of nodulisporic acid A
- Developed second-generation strategy based on sequential Stille cross-coupling/
Buchwald-Hartwig union
- Progress towards the total synthesis continues