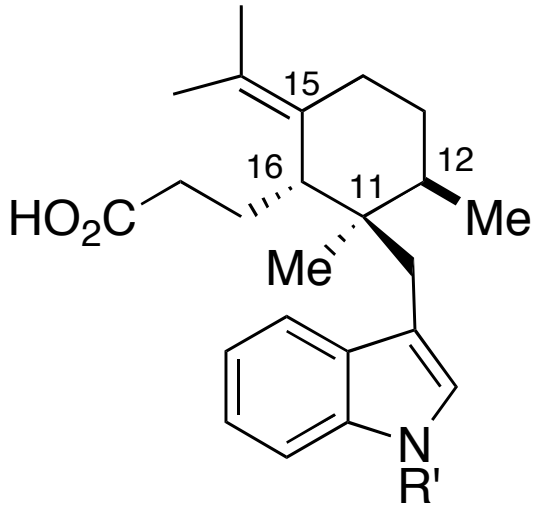
Total Synthesis of (+)-Suaveolindole



Emile J. Velthuisen and Samuel J. Danishefsky

J. Am. Chem. Soc. 2007, *129*, 10640-10641

Julia Vargas

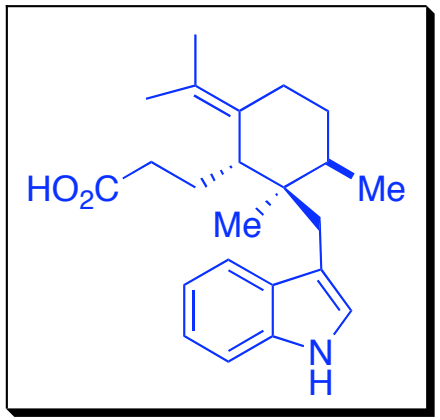
September 15, 2007

Outline

- Isolation and Elucidation of (+)-Suaveolindole
- Biological activity
- Overview of Indole Ring Syntheses
- Syntheses of Indolosesquiterpenes
- Total synthesis of (+)-Suaveolindole
- Summary

(+)-Suaveolindole

- Isolated from *Greenwaydendron suaveolens*
  - *Annonaceae* or "custard apple family"
    - flowering trees and shrubs
    - found in tropical, temperate regions of Africa
    - aromatic terpenoids and benzyl isoquinoline alkaloids
- Novel indolosesquiterpene structure
- Structure elucidation by 1D and 2D-NMR, HRESIMS, UV
  - IR and optical rotation not able to be determined



J. Nat. Prod. **2005,** *68,* 122-124

http://en.wikipedia.org/wiki/Image:Annona_squamosa.jpg

http://www.ruhr-uni-bochum.de/boga/html/Brugmansia_suaveolens_Foto.html

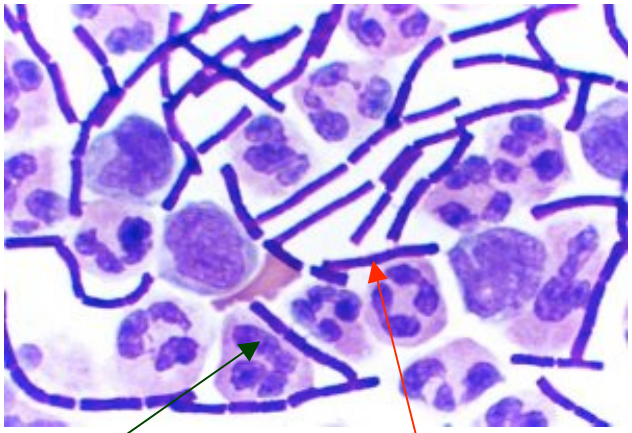
Biological Activity

- Potent activity against gram positive bacteria

Bacillus subtilis (MIC) 4 μg/mL

Staphylococcus aureus 8 μg/mL

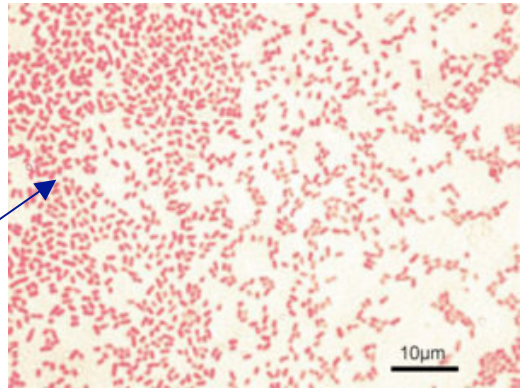
Staphylococcus aureus methicillin resistant 8 μg/mL



- Not active against gram negative bacteria

Klebisella pneumoniae 128 μg/mL

Pseudomonas aeruginosa 128 μg/mL



(pictures of gram positive and negative bacteria taken from Wikipedia.org)

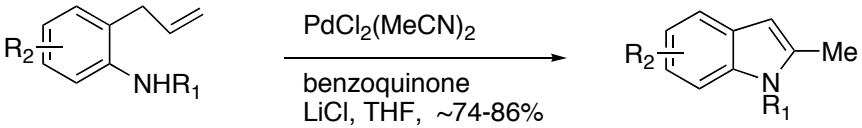
J. Nat. Prod. **2005,** *68,* 122-124

Indole Ring Syntheses

Gribble, G.W. *J.Chem. Soc., Perkin. Trans. 1,* 2000, 1045

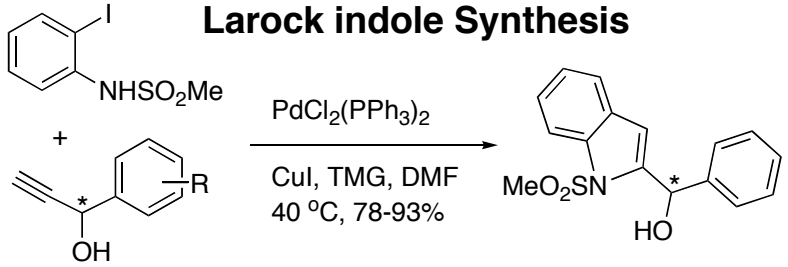
Metal Mediated Cyclizations

Hegedus-Mori-Heck indole Synthesis

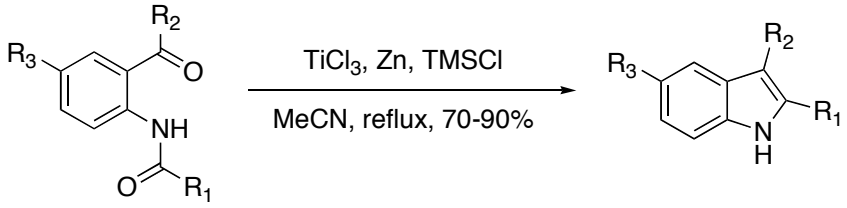


R_1 = H, Me, Ac
R_2 = H, 5-Me, 5-CO_2Et, 6-OMe

Larock indole Synthesis

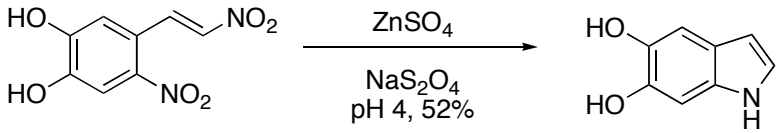


Fürstner Indole Synthesis



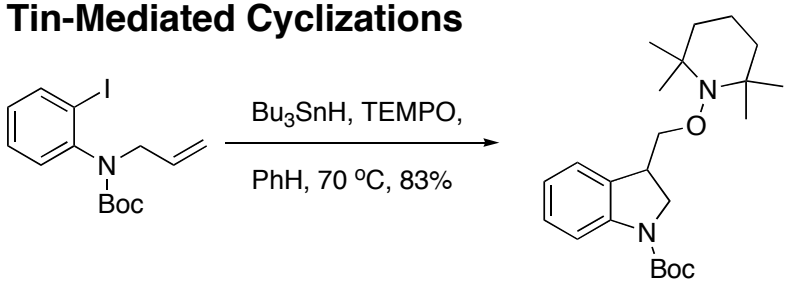
Reductive Cyclizations

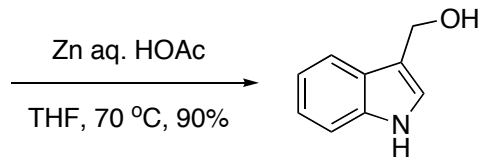
o, β–Dinitrostyrene reductive cyclization



Radical Cyclizations

Tin-Mediated Cyclizations



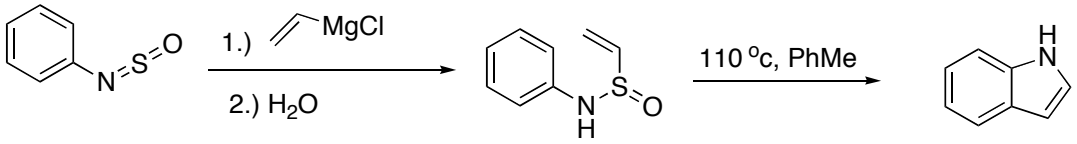


Indole Ring Syntheses

Gribble, G.W. *J.Chem. Soc., Perkin. Trans. 1,* 2000, 1045

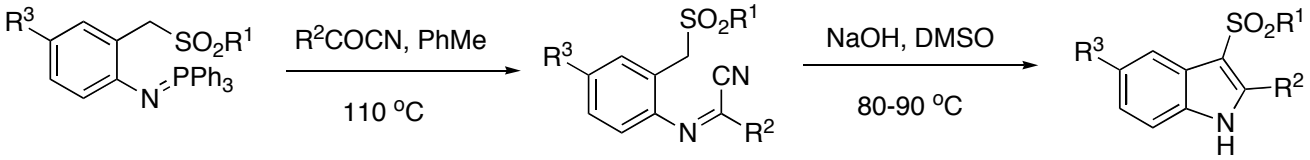
Sigmatropic Rearrangements

Julia indole Synthesis



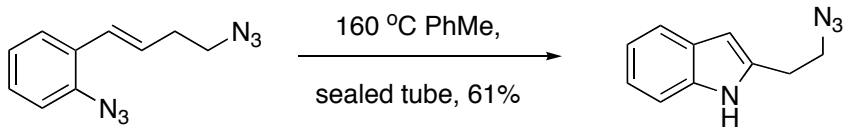
Nucleophilic Cyclizations

Aza-Wittig Reaction



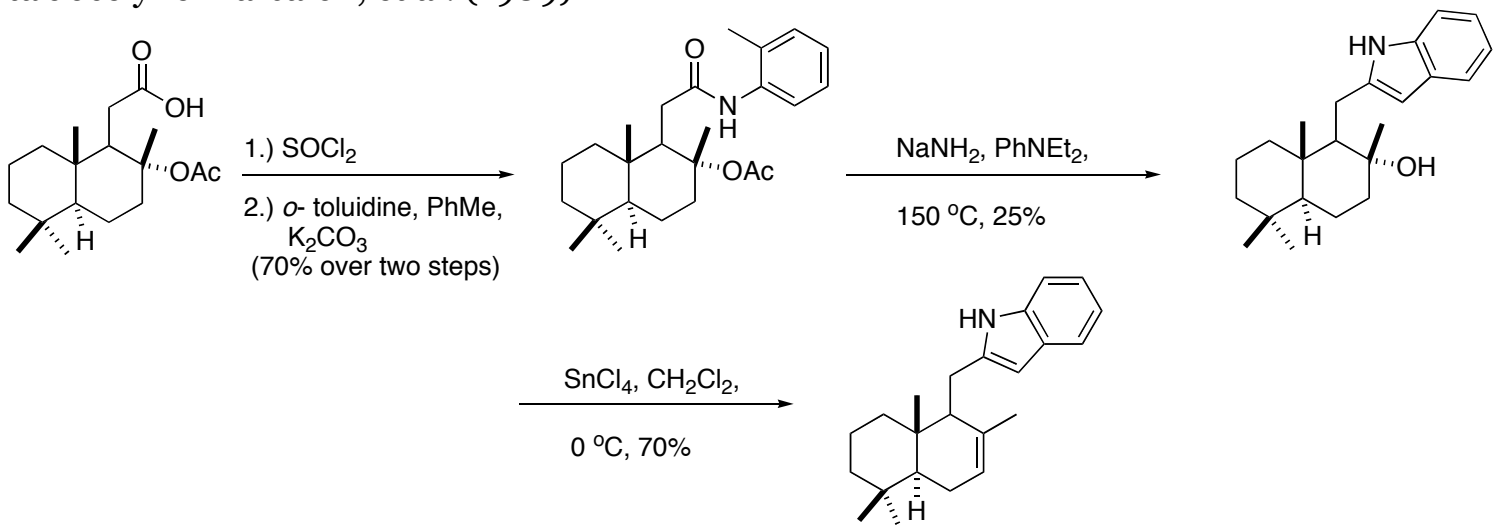
Electrophilic Cyclizations

Sundberg indole Synthesis

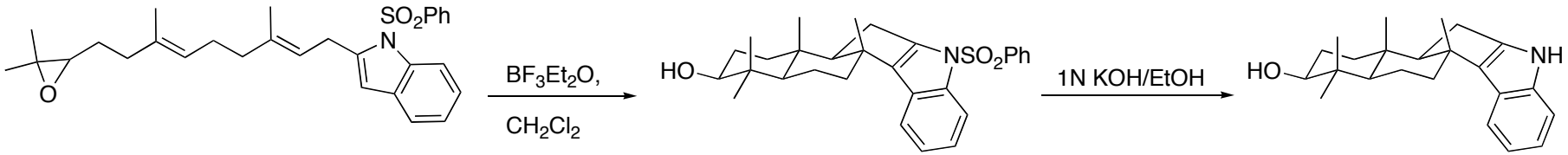


Indolosesquiterpenes

Anita Jocelyne Marsaioli, et al. (1989)



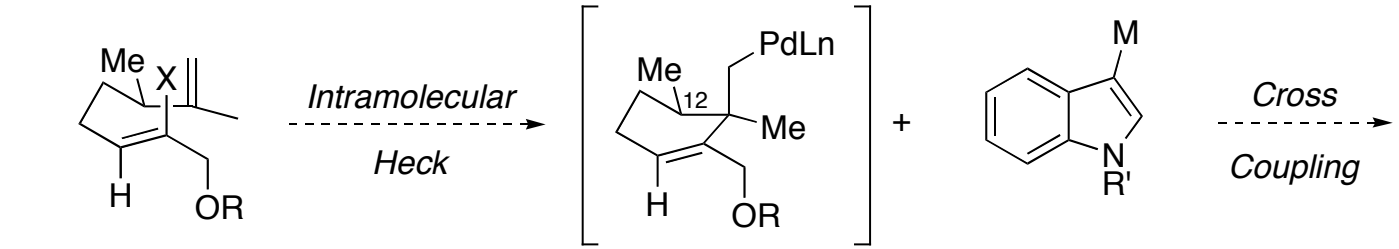
Catherine Mirand, et al. (1987)



Polyveoline

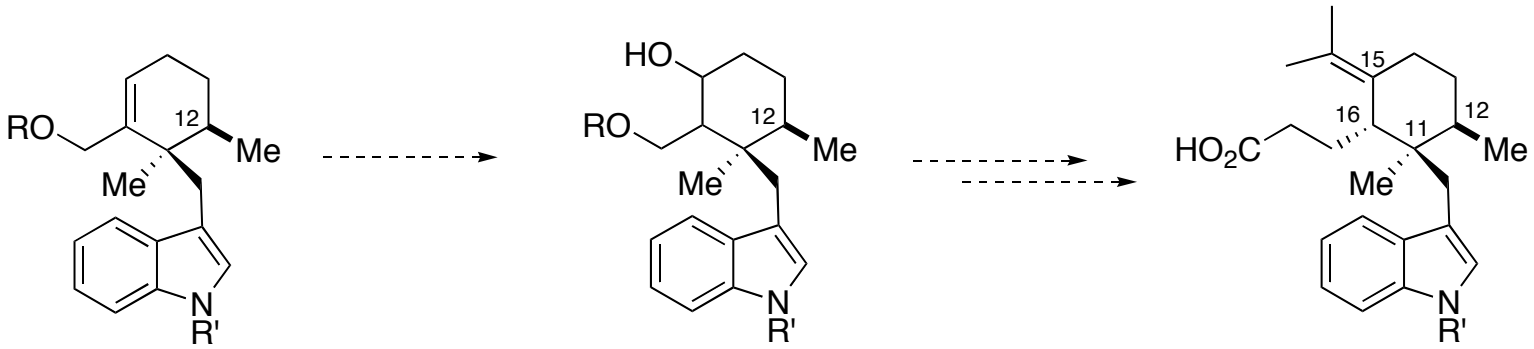
C. Mirand et. Al., *Tet. Lett.*,1987, 28(31), 3565-3568; Marsaioli, A.J. et. Al, *J.Chem.Soc. Perkin. Trans. 1,* 1989, 559

Initial synthetic strategy…

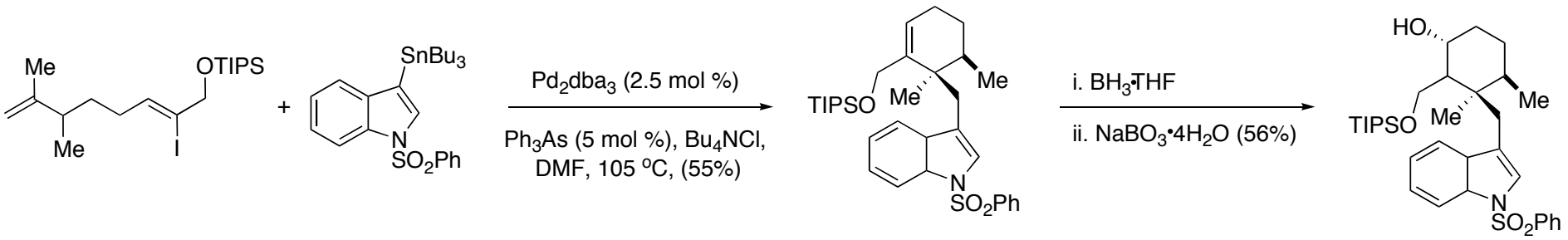


X: I or PdLn

M: SnR_3, BR_2

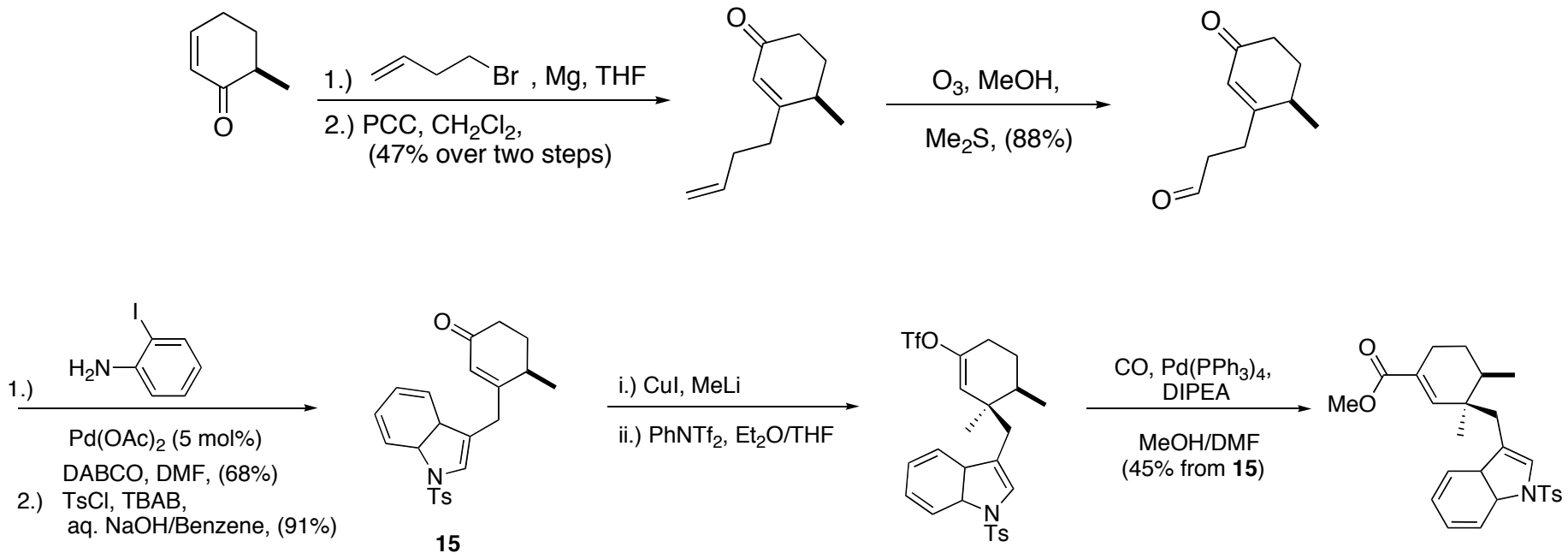


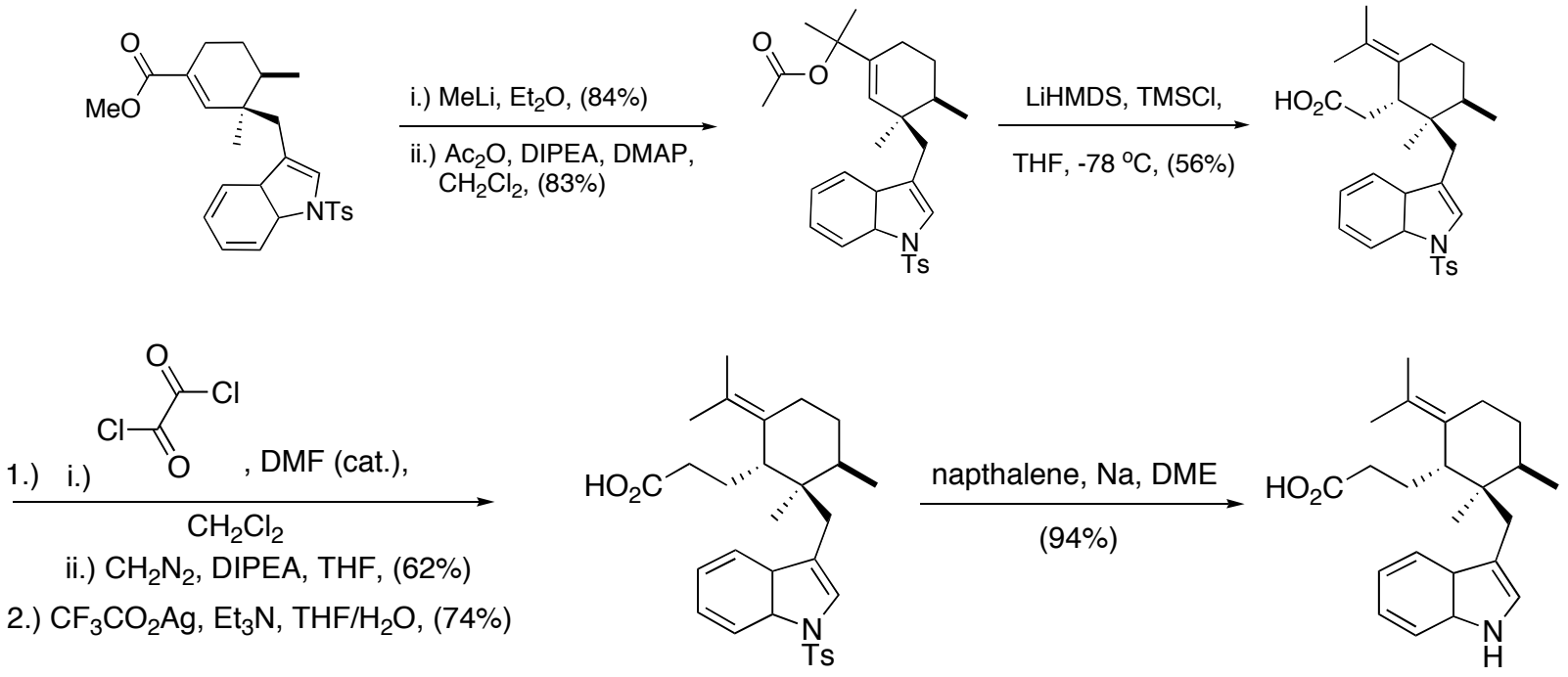
Suaveolindole



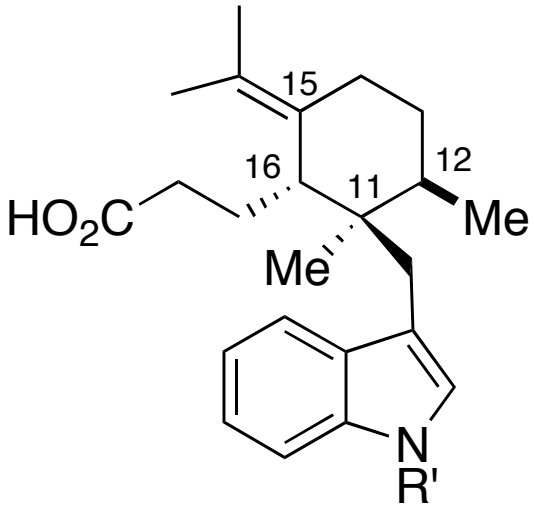
(4:1 dr)

The winning approach...




MeO
NTs
i.) MeLi, Et2O, (84%)
ii.) Ac2O, DIPEA, DMAP,
CH2Cl2, (83%)
LiHMDS, TMSCl,
THF, -78 °C, (56%)
HO2C
1.) i.)
, DMF (cat.),
CH2Cl2
ii.) CH2N2, DIPEA, THF, (62%)
2.) CF3CO2Ag, Et3N, THF/H2O, (74%)
napthalene, Na, DME
(94%)
(+)-Suaveolindole

Summary



- Completed the first total synthesis of (+)-Suaveolindole
- 13 steps, 1.9% overall yield
- Determined optical rotation:

  Sequoia Sciences (isolated): $[\alpha]^{22}_{D}$= +26° (*c* = 1.0, CH_3OD)

  Synthetic Sample: $[\alpha]^{22}_{D}$= +32° (*c* = 1.0, CH_3OD)
- Determined Absolute Configuration (R,R,S) for C_{11}, C_{12}, C_{16} respectively
- Synthetic sample exhibits comparable biological activity as reported for naturally occurring (+)-Suaveolindole