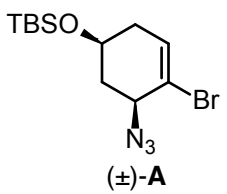
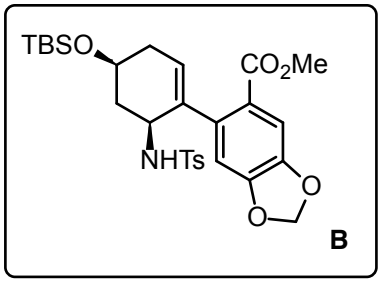
Biomimetic Total Synthesis of the Pentacyclic *Amaryllidaceae* Alkaloid Derivative Gracilamine

Nadia (Yuqian) Gao, Martin G. Banwell and Anthony C. Willis, *Org. Lett.* **2017**, *19*, 162–165.

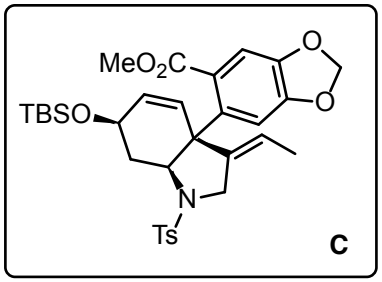


(±)-**A**

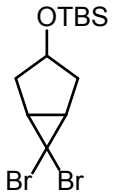
1-3



4-5



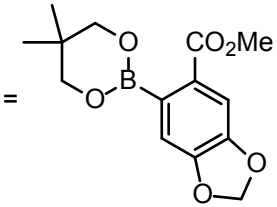
6-9



X

1) PPh_3, MeOH/H_2O
2) TsCl, NEt_3
3) **Y**, $PdCl_2dppf{\bullet}CH_2Cl_2$, KOAc, Cs_2CO_3,

Y =

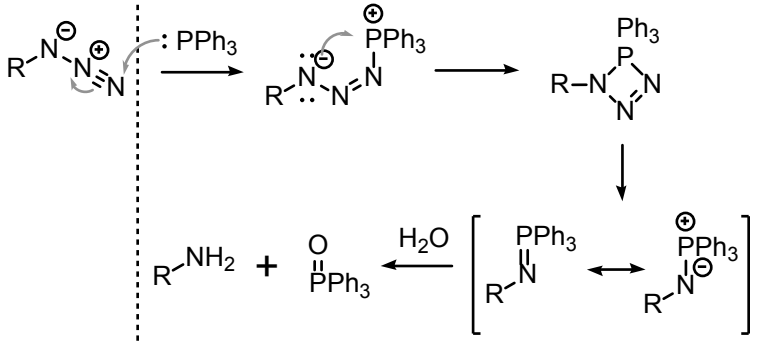


4) NaH, 1-bromo-2-butyne
5) $Pd(OAc)_2$, *N,N'*-Dibenzylideneethylenediamine, toluene, reflux

6) DIBAL-H
7) DMP
8) ethyl L-Leucinate•HCl, Et_3N, $MgSO_4$
9) toluene, reflux

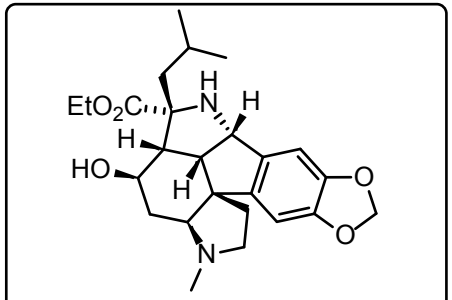
The starting material can be prepared within 2 steps from the [3.1.0]-bicylce **X.** Please think of a possible transformation and the mechanism.

Please sketch the mechanism of the reaction in step 1.

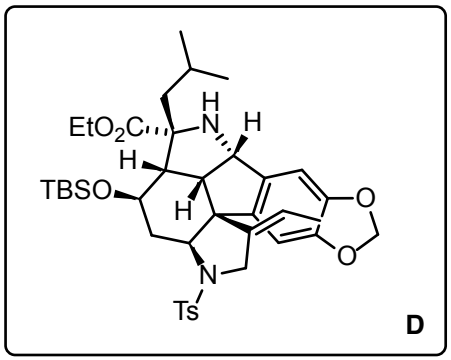


Please provide the name and a detailed mechanism for the reaction in step 5. Could you think of a possible side product (38 %)?

Pd(II)-catalyzed intramolecular Alder-ene (IMAE) reaction



(±)-Gracilamine



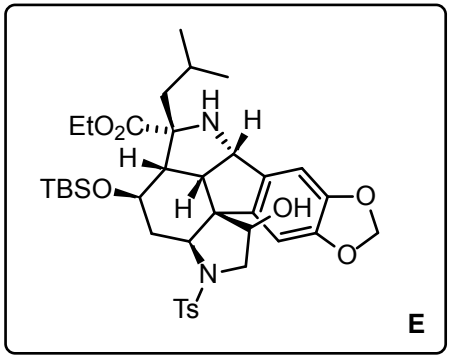
D

10-12

10) $K_2OsO_4 \cdot 2\ H_2O$ (10 mol%), NMO (2 eq), citric acid
11) $PhI(OAc)_2$
12) $NaBH_4$

What is the role of citric acid in step 10?
- neutralizing the emerging *N*-methyl morpholine in order to maintain the ideal pH[1]
- ligand for Os(VI), keeping the catalytically active species in solution and stabilizing it from disproportionation[1]

1) *Adv. Synth. Catal.* **2002**, *344*, 421–433.

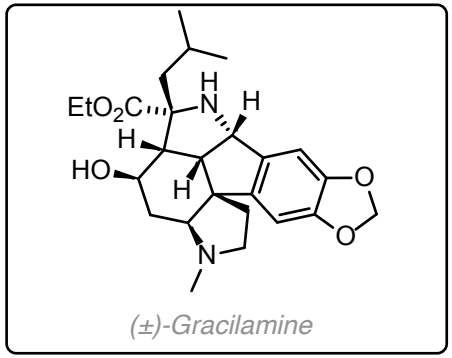


E

13-16

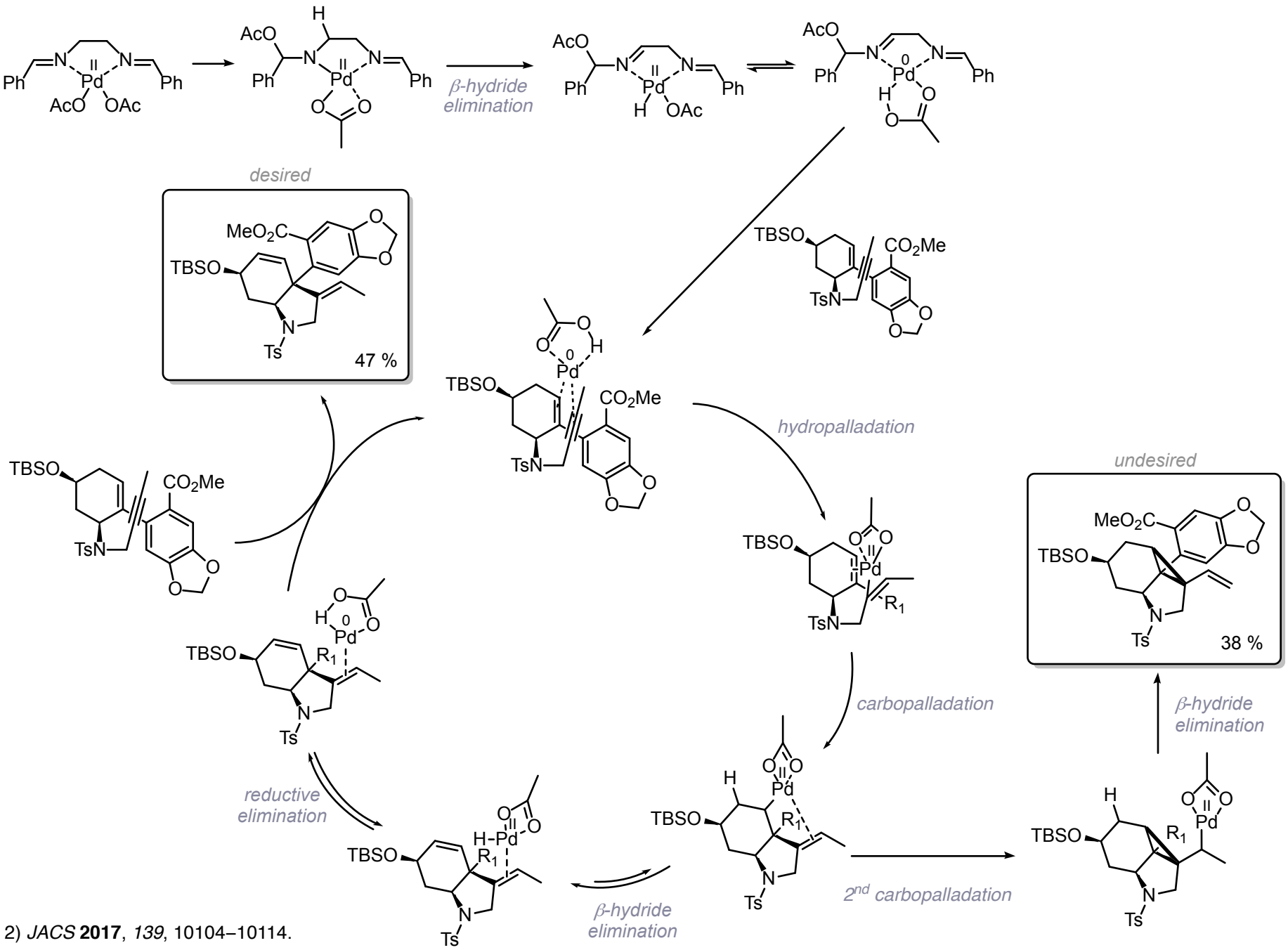
13) NaH, CS_2, MeI
14) *n*-Bu_3SnH, AIBN
15) Mg, MeOH, sonication
then HCl (aq.)
16) H_2CO, $NaCNBH_3$

Please provide a detailed mechanism for the transformation of step 14.



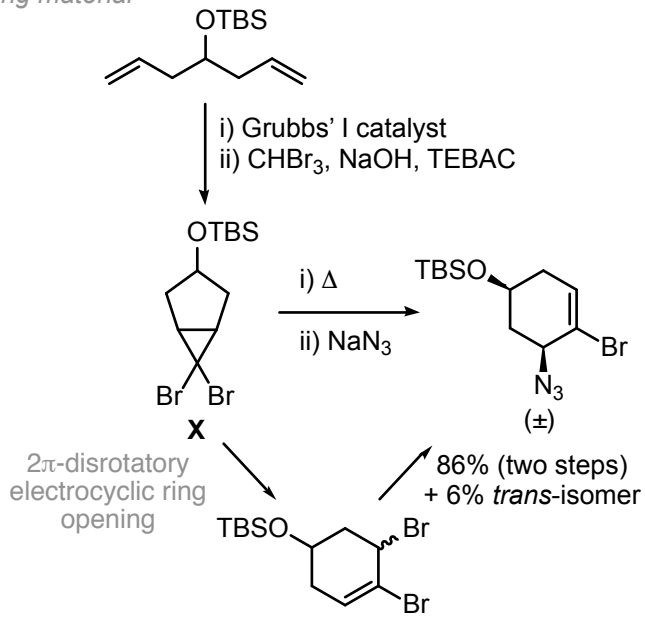
(±)-Gracilamine

Mechanism of the Pd(II)-catalyzed IMAE[2]



2) *JACS* **2017**, *139*, 10104–10114.

Starting material[3]



TEBAC = triethylbenzylammonium chloride

3) Org. Lett. **2001**, *13*, 5800–5803.

Barton McCombie-deoxygenation