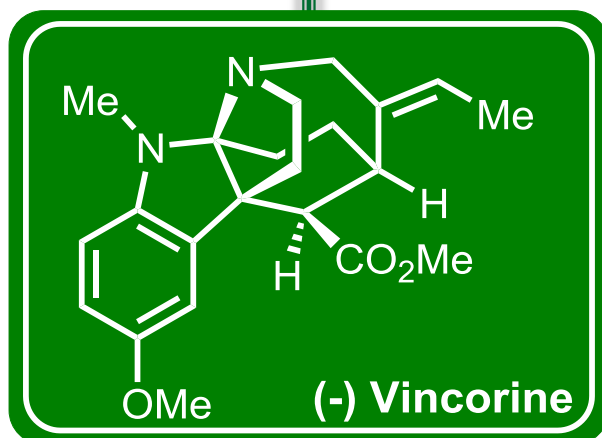


Total Synthesis of (-) Vincorine

Proposed by Gilles Galvani – Equipe CoSMIT, Postdoc Lermite



➤ **Vinca alkaloid natural products** exhibit diverse pharmacological properties which have been studied for the development of anticancer agents (vinblastine), vasodilators (vincamine), antipsychotics and anti-hypertensives (reserpine).

➤ **(-) Vincorine** is a compound of this family which presents a singular tetracyclic core constituted by a **strained 7 membered azepanyl ring fused with a pyrroloindole motif**. Potential anti-cancer activity of this molecule is under investigation.

➤ **3 Total Syntheses** of Vincorine have been realized :

* **Qin** et al., JACS 2009, 131, 6013-6020

Racemic, 35 steps, 1 % overall yield

Key steps: Iminium cyclisation; Cu(I) cat. Cyclopropanation; Mukaiyama.

* **Ma** et al., JACS 2012, 134, 9126-9129

18 steps, 5 % overall yield, 64 % ee

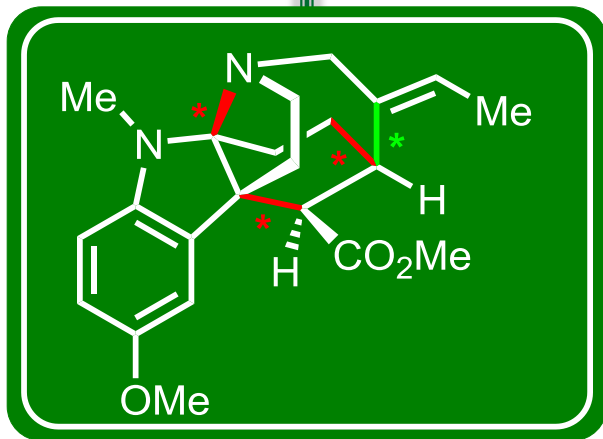
Key steps: Iminium cyclisation; Asymmetric Michael; Oxidative coupling.

➤ **The last one** is the purpose of the present Total Synthesis Problem. Based on an efficient organocatalytic key step, it prevails as the most valuable synthesis strategy.

* **MacMillan** et al.

9 steps, 9 % overall yield, 95 % ee

Key steps: Catalytic cascade cyclisation, 9-membered azepanyl ring cyclisation



* Enantioselective
Organocatalytic Cascade

* Seven membered Azepanyl
formation

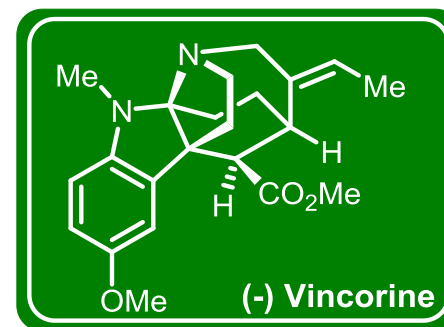
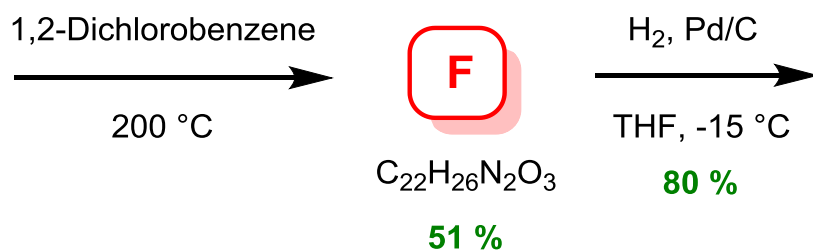
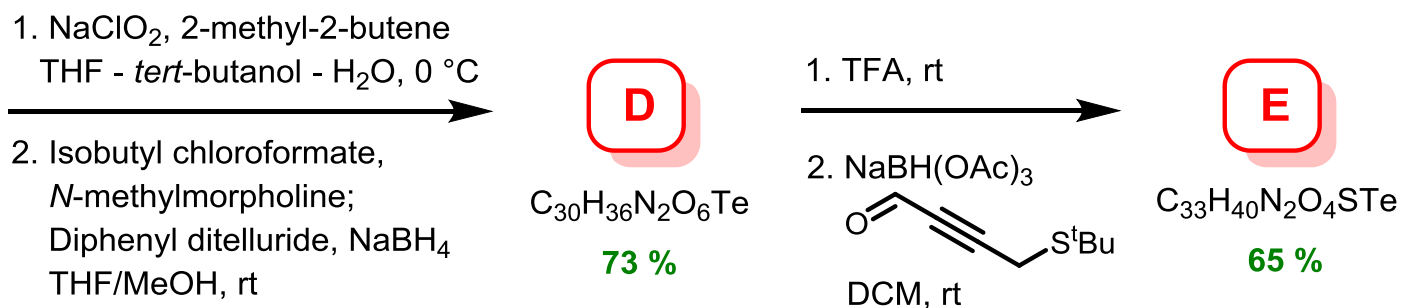
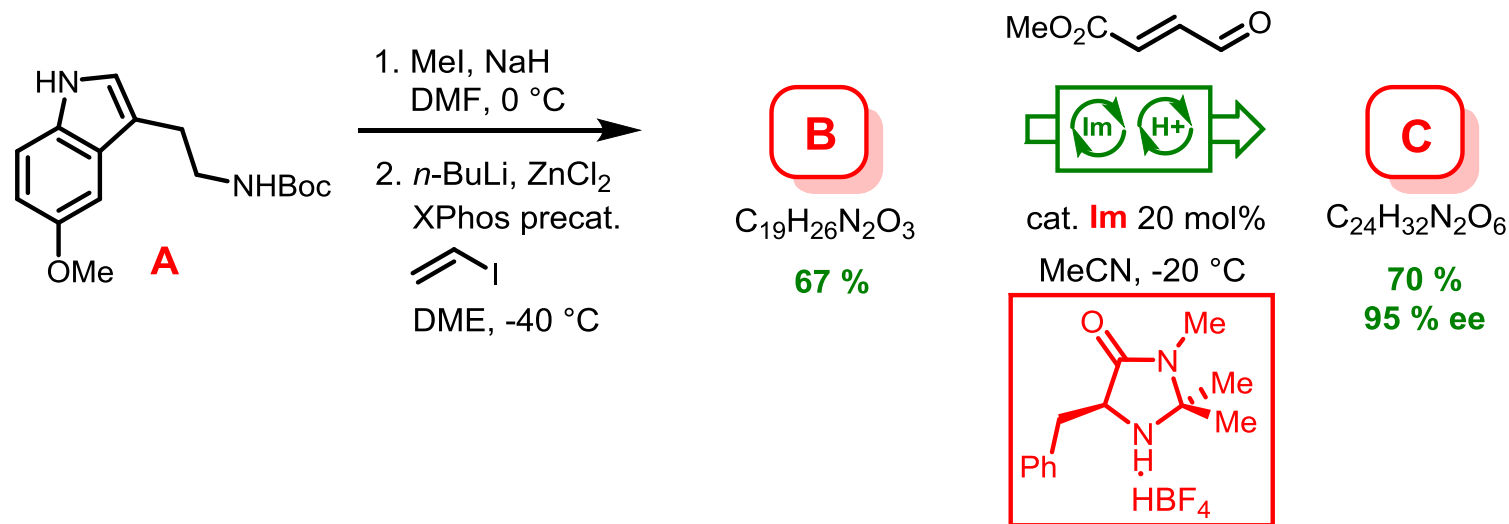
➤ Questions :

✓ Find structures of **B**,
C, **D**, **E** & **F**.

✓ Propose a pathway
for imidazolidinone
catalytic event.

✓ Which transition
state could explain
excellent
enantioselectivity of
tetracyclic product
C formation ?

✓ Mechanism of
transformation from
D to **E** ?



9 % over 9 steps