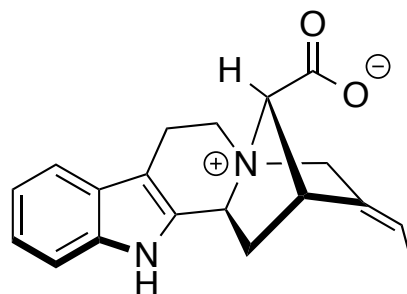


Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for the Total Synthesis of (-)-17-nor-Excelsinidine

Jarret M., Tap A., Kouklovski C., Poupon E., Evanno L., Vincent G., *Angew. Chem. Int. Ed.* 10.1002/anie.201802610



Emy André-Joyaux
Renaud Group
University of Bern
19th April 2018

u^b

^b
UNIVERSITÄT
BERN

Guillaume Vincent

Education:

- Ecole Supérieure de Chimie Physique et Electronique (one year at the Dupont Pharmaceuticals Company in Wilmington - USA) and M. Sc. Degree from Université Lyon I in the group of Prof. Ciufolini in 2002
- Ph.D. under the supervision of Prof. Marco A. Ciufolini in 2005

Professional and academic experience:

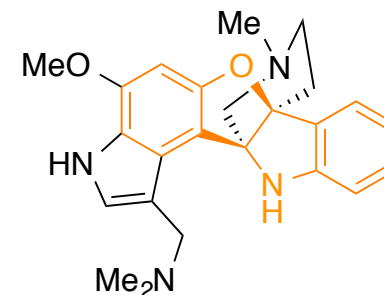
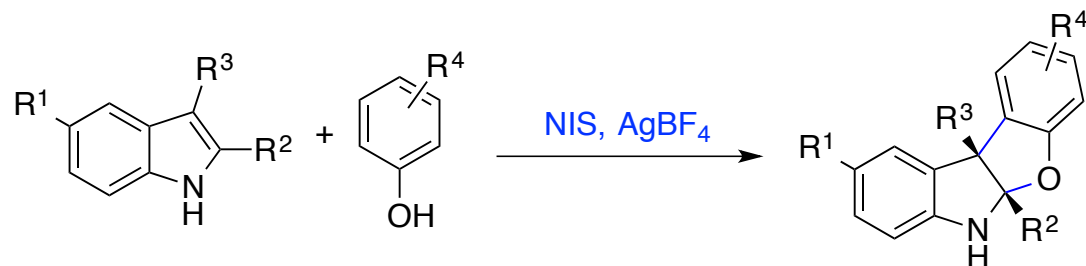
- Postdoral associate at Colorado State University in the group of Prof. Robert M. Williams
- Research at the University Pierre et Marie Curie (Paris 6) in the group of Prof. Max Malacria and Prof. Louis Fensterbank in 2007
- Chargé de Recherche at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (University Paris Sud)
- Independant research program towards the reactivities of the indole nucleus, in 2011



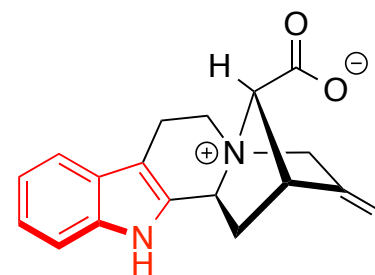
Guillaume Vincent

Methodological interests:

- Total synthesis of benzofuroindoline containing natural product
- Development of oxidative coupling between phenol and indole
- Total synthesis of indole alkaloids

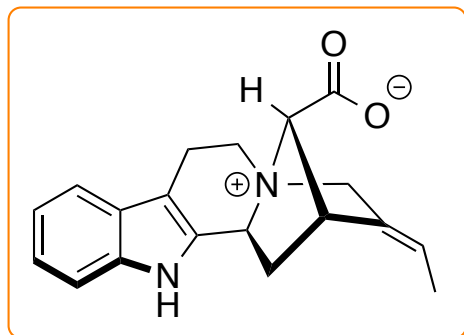


phalarine
Phytochemistry **1999**, 51, 153-157

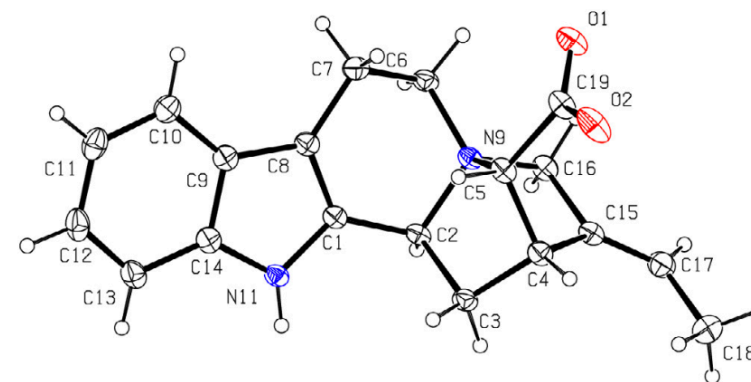


(-)-17-nor-Excelsinidine
Angew. Chem. Int. Ed. **2018**, just accepted

Introduction



(-)-17-nor-Excelsinidine

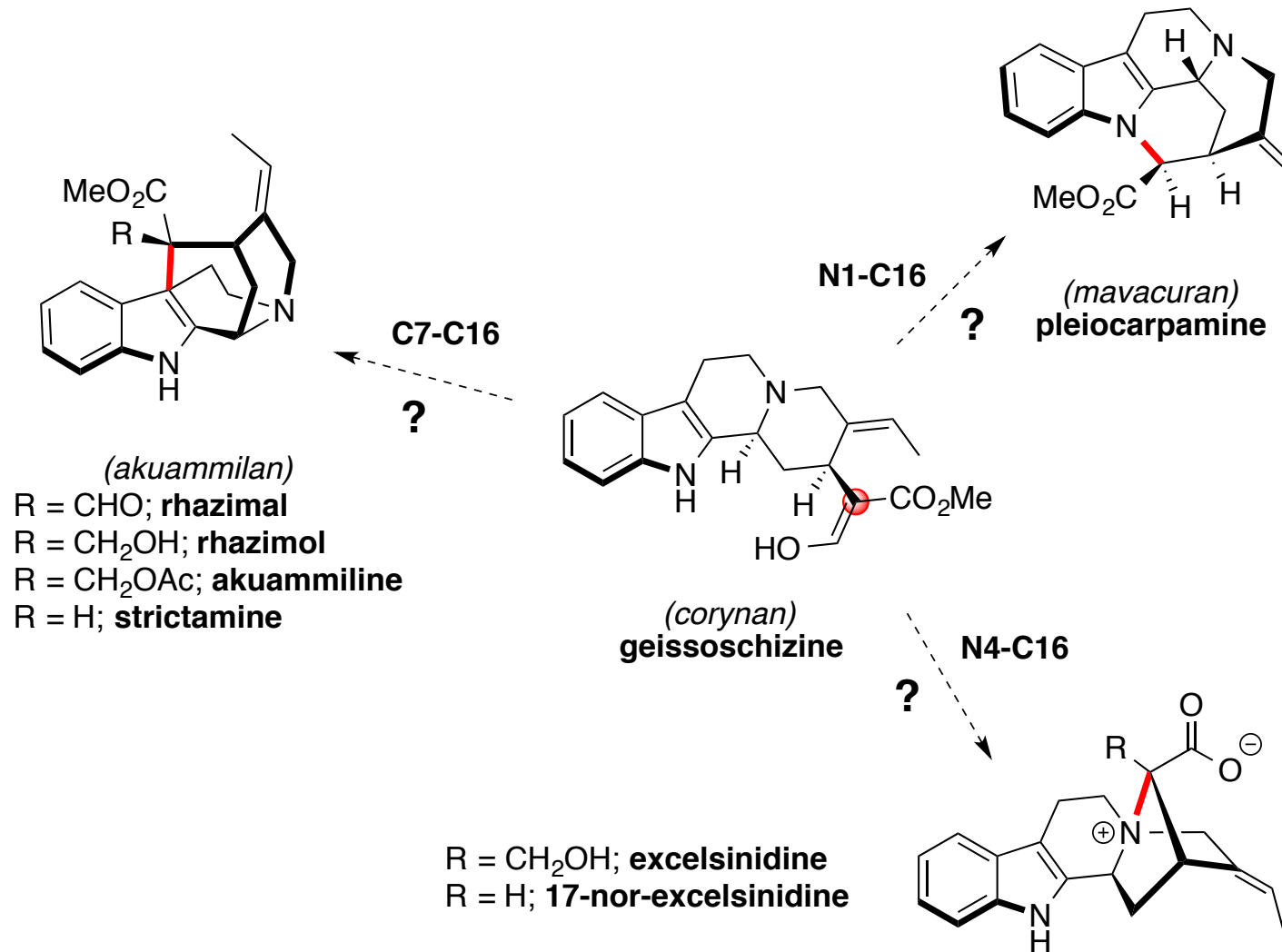


X-ray structure of (-)-17-nor-Excelsinidine¹

- Isolated in 2014 from the twigs and leaves of *Alstonia scholaris*¹
- Bridged bicyclic ammonium moiety
- Display anti-adenovirus and anti-HSV¹
- Absolute stereochemistry determined by NMR spectroscopy and X-ray crystallography
- No previous total syntheses reported

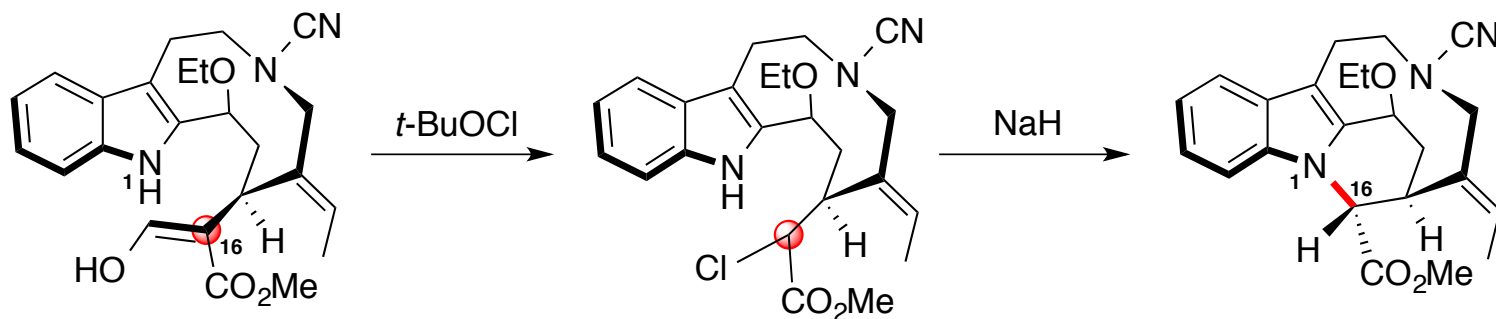
¹Tetrahedron Lett. **2014**, *55*, 1815–1817

Postulated biosynthesis of Excelsinidines

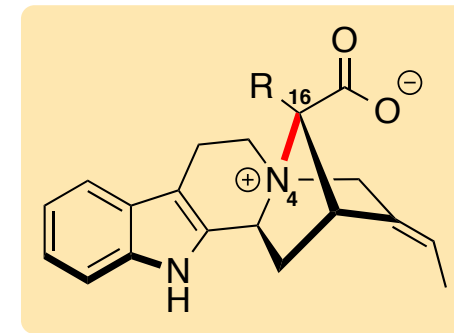
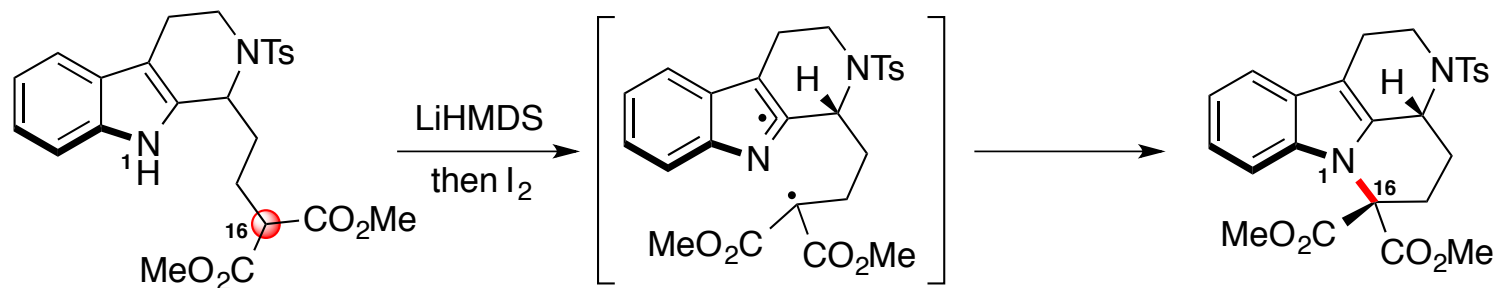


Previous studies

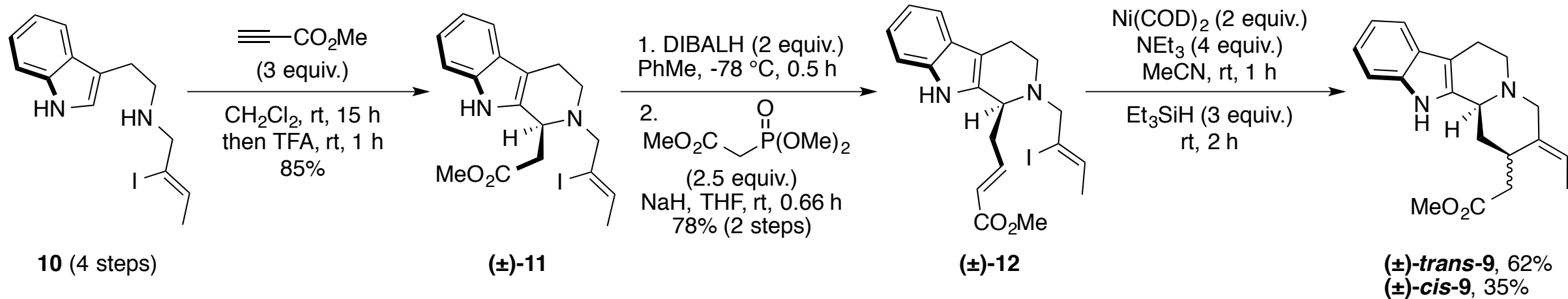
Sakai - Oxidative chlorination/Nucleophilic substitution



Zhu - *bis*-deprotonation/Oxidation into a biomimetic *bis*-radical intermediate

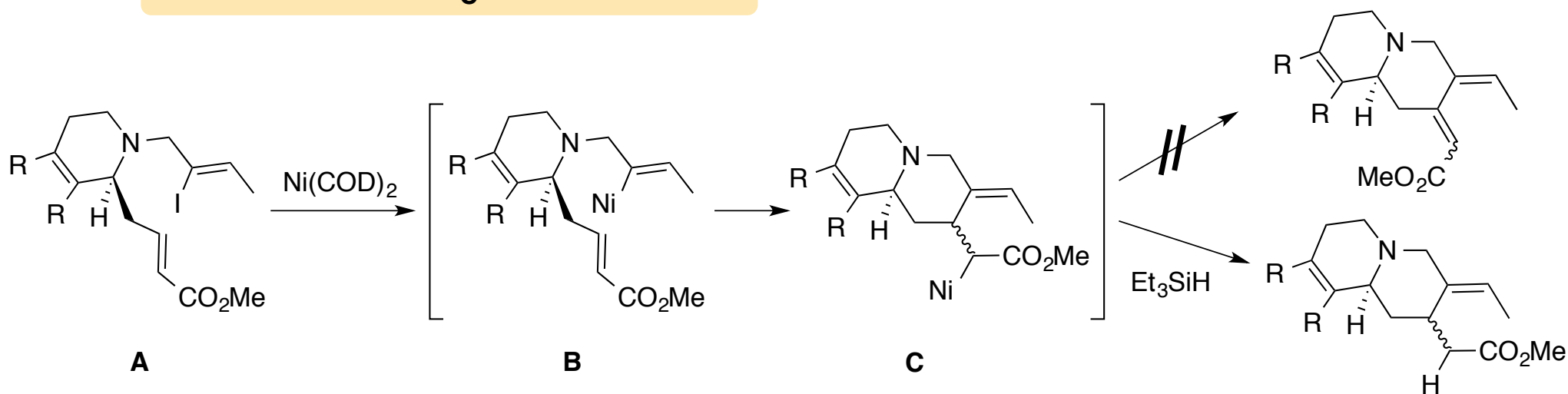
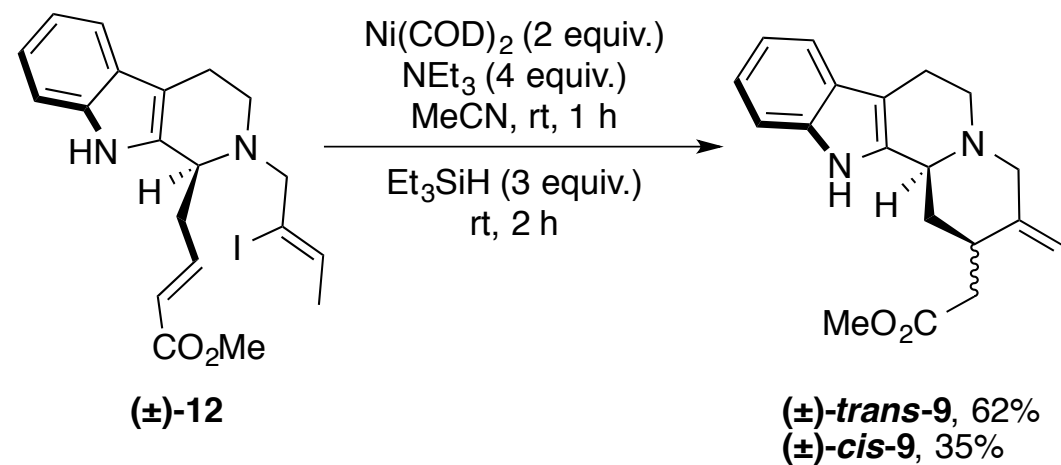
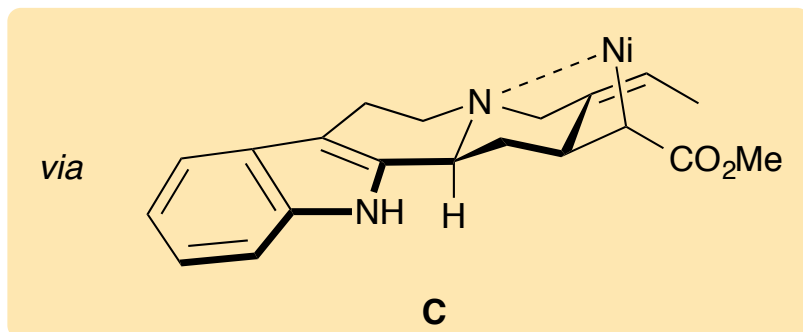


Synthesis of (±) and (+)-16-desformyl-geissoschizine

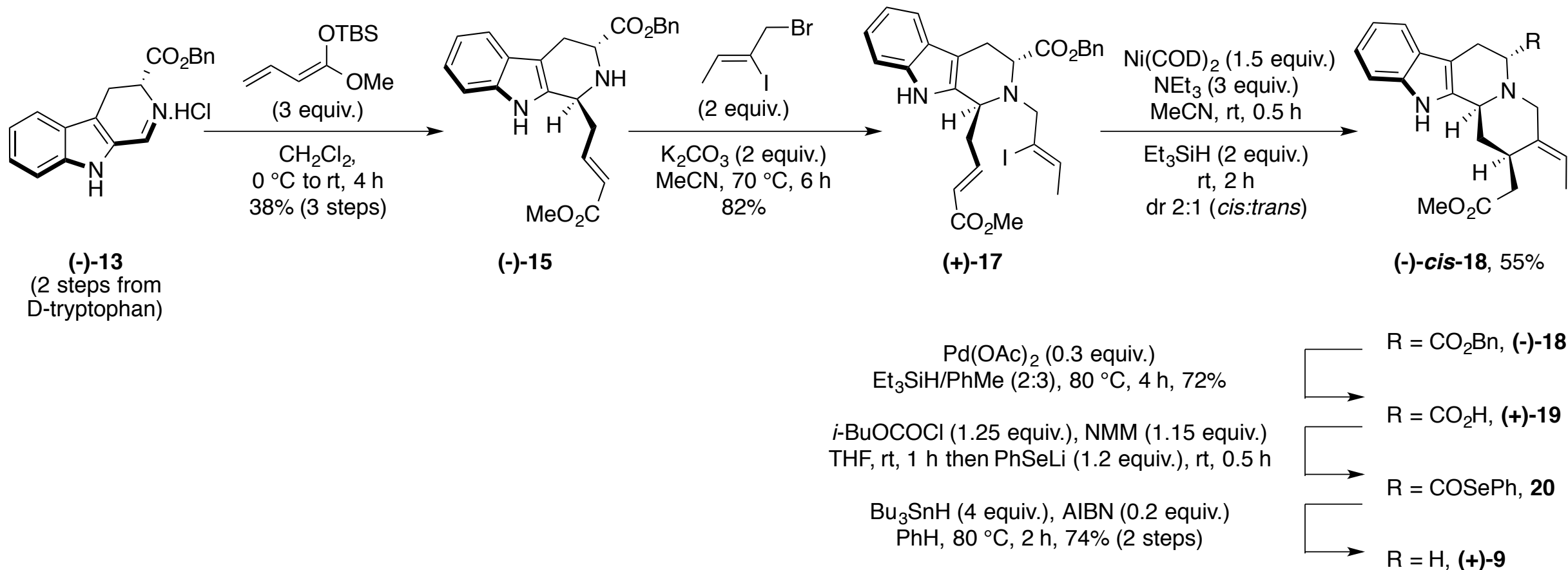


Synthesis of (±) and (+)-16-desformyl-geissoschizine

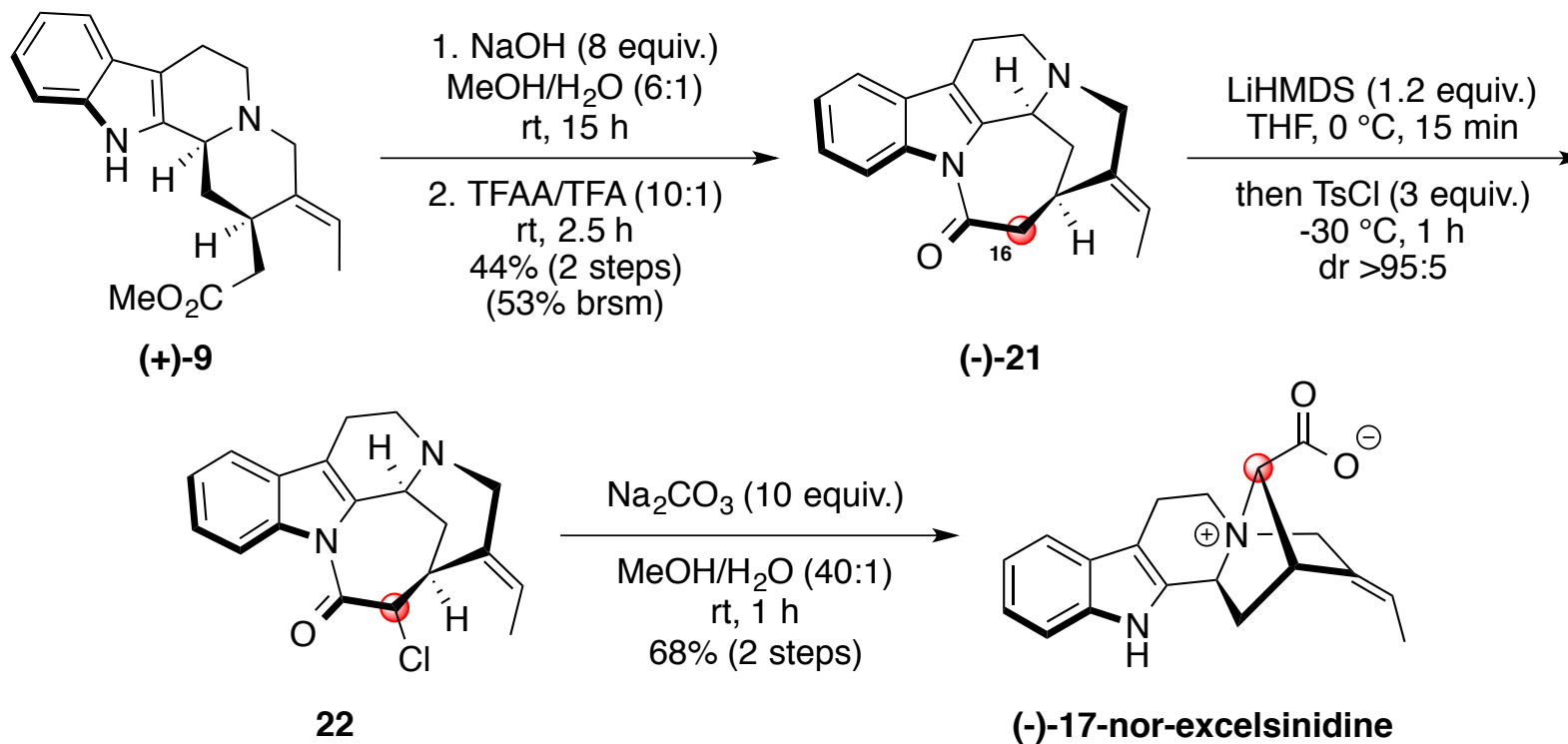
Nitrogen Assistance in Intramolecular Nickel-Promoted Tandem Cyclization



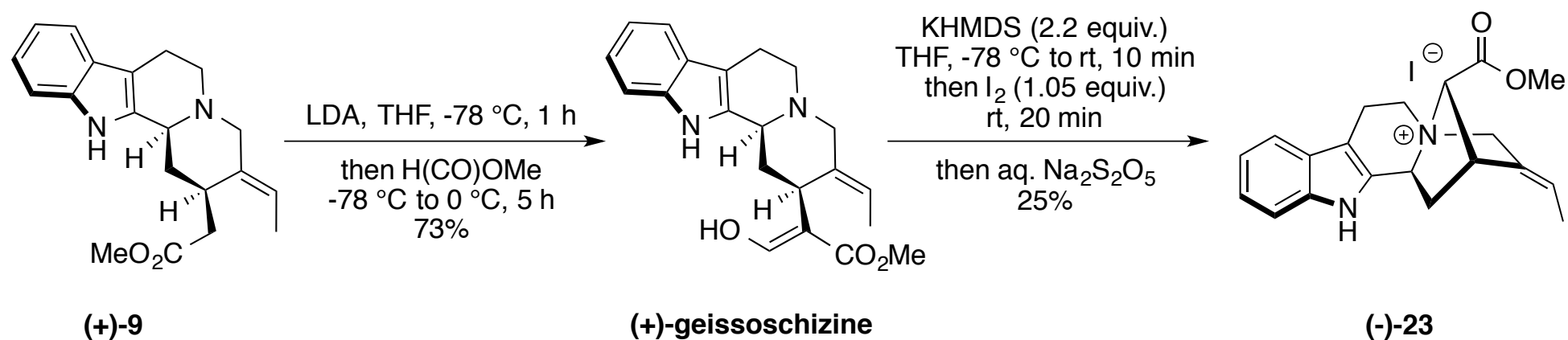
Synthesis of (±) and (+)-16-desformyl-geissoschizine



End game

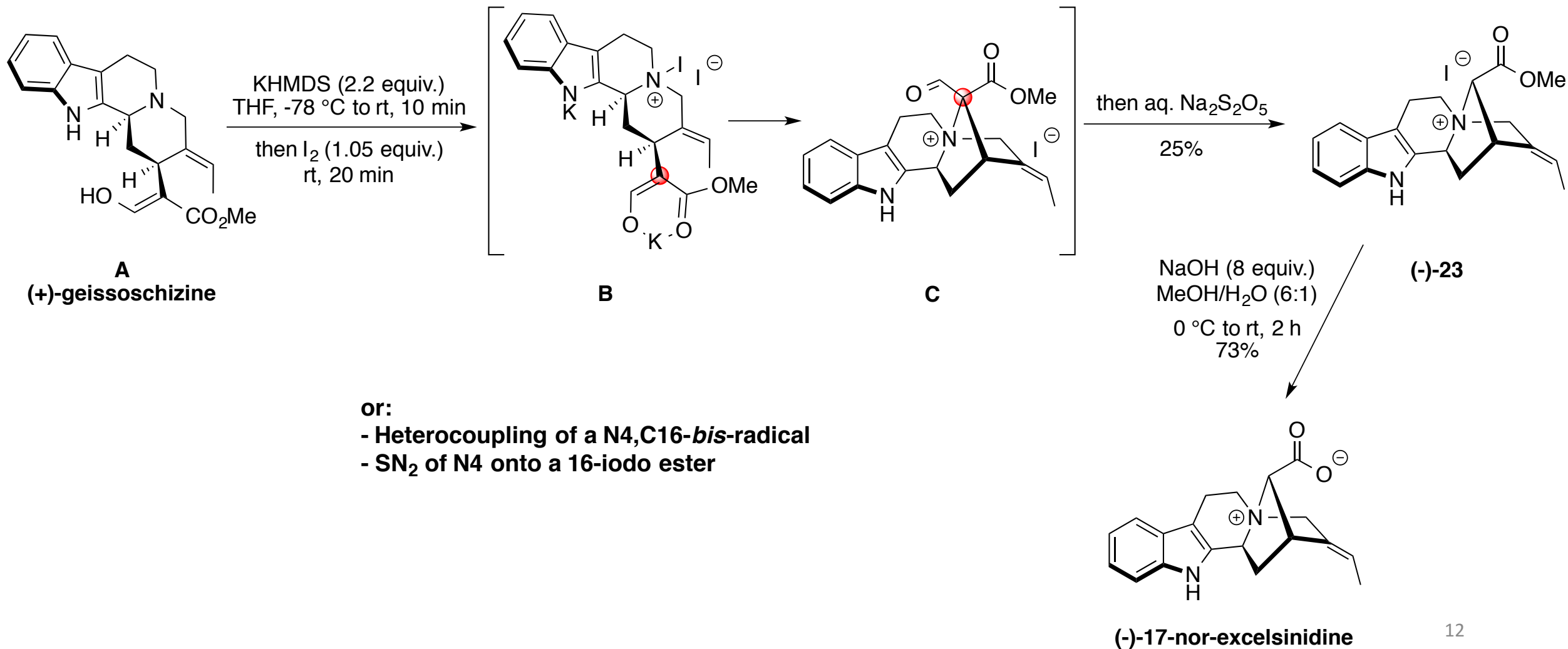


Direct oxidative cyclization of geissoschizine



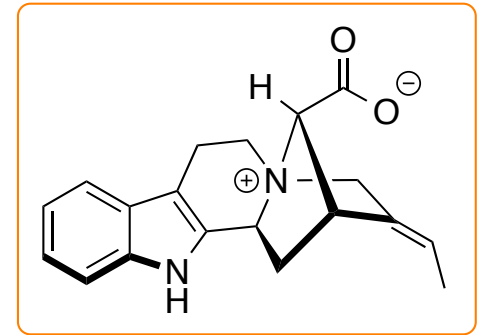
Direct oxidative cyclization of geissoschizine

Plausible mechanism:

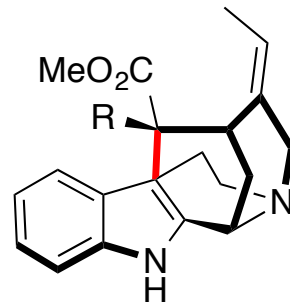


Conclusion

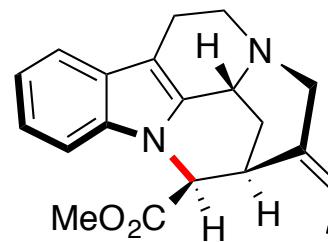
- First total synthesis of (+)-17-nor-Excelsinidine
- Overall yields:
 - Through (+)-16-desformyl-geissoschizine: 2,7% over 12 steps
 - Through (+)-geissoschizine: 1,2% over 11 steps
- Two oxidative cyclization leading to the formation of N4-C16 bond



(-)-17-nor-Excelsinidine



C7-C16
(akuammilan)



N1-C16
(mavacuran)