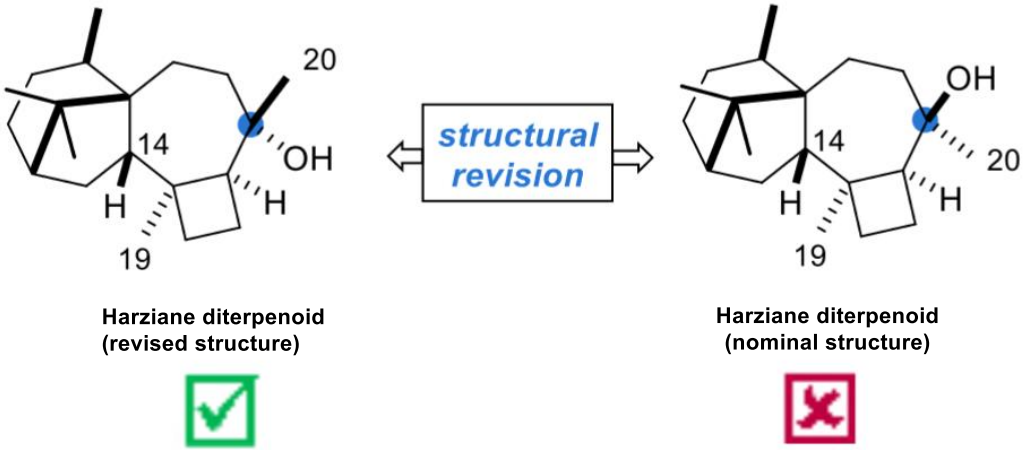
Total Synthesis and Structural Revision of a Harziane Diterpenoid

Moritz Hönig and Erick M. Carreira
Angew. Chem. Int. Ed. 10.1002/anie.201912982



Journal Club
Renaud Group
Dace Cirule
13.11.2019

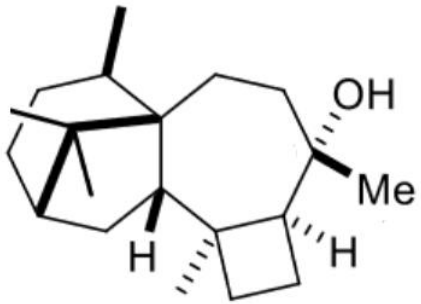
Erick M. Carreira

- PhD at Harvard University, 1990 (David A. Evans)
- PostDoc at Caltech, 1992 (Peter Dervan)
- Assistant Professor to full Professor at Caltech 1992-1997
- Full Professor at ETH Zurich since 1998

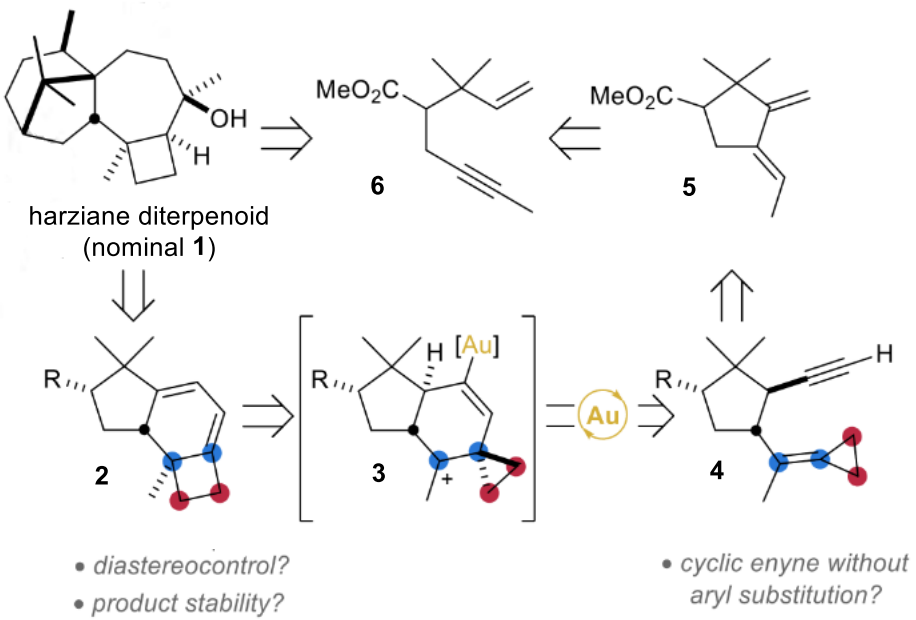
Research: asymmetric synthesis of biologically active, stereochemically complex, natural products

Harziane Diterpenoids

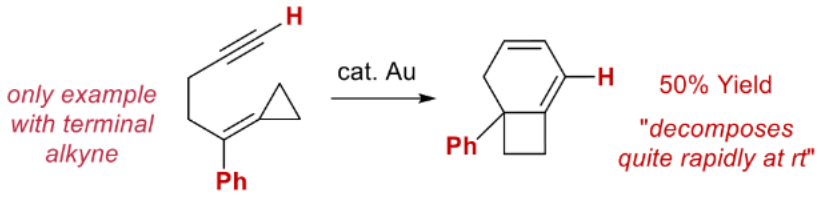
- Secondary metabolites – isolated from *Trichoderma* fungi
- 8/10 isolated members contain the unique 6–5–7–4 carbon skeleton
- Antifungal and cytotoxic activity
- No reported synthetic studies



Retrosynthesis

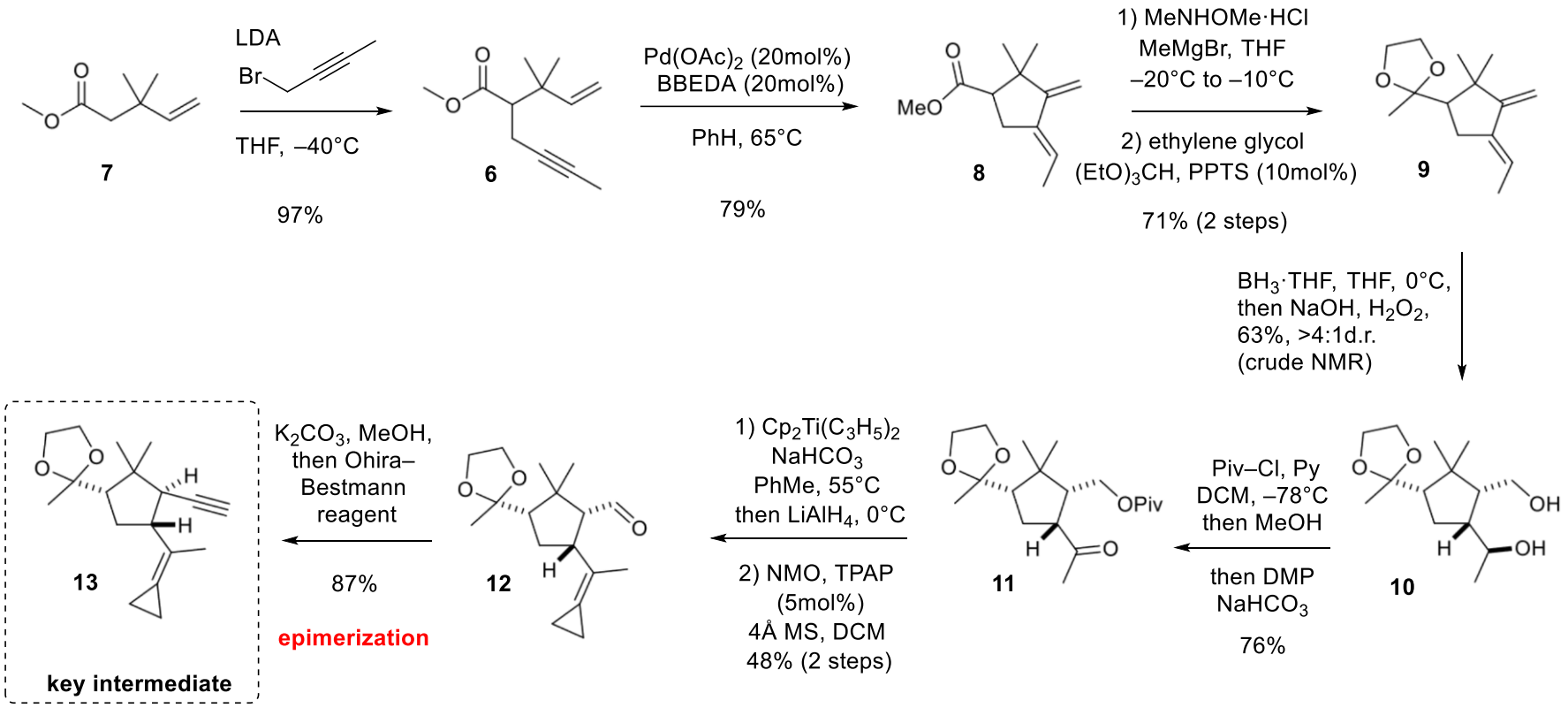


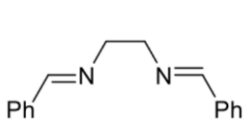
Previous work by Gagne:



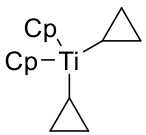
Org. Lett. **2014,** *16*, 2272-2275

Synthesis of the key intermediate

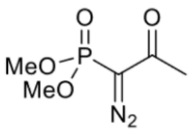




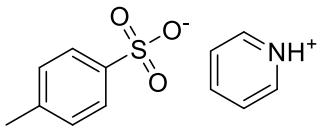
BBEDA



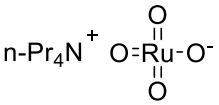
Petasis dicyclopropyl reagent



Ohira–Bestmann reagent

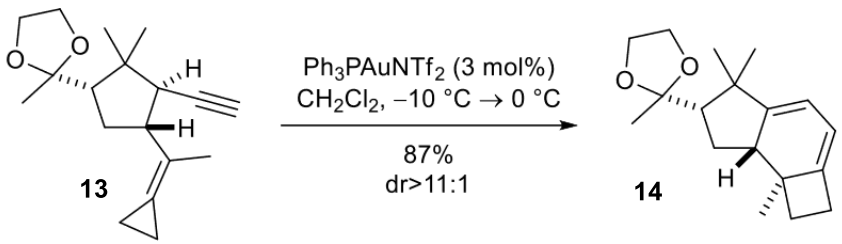


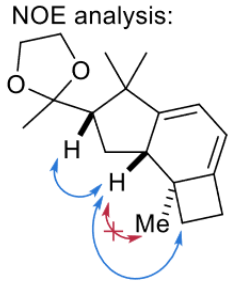
PPTS

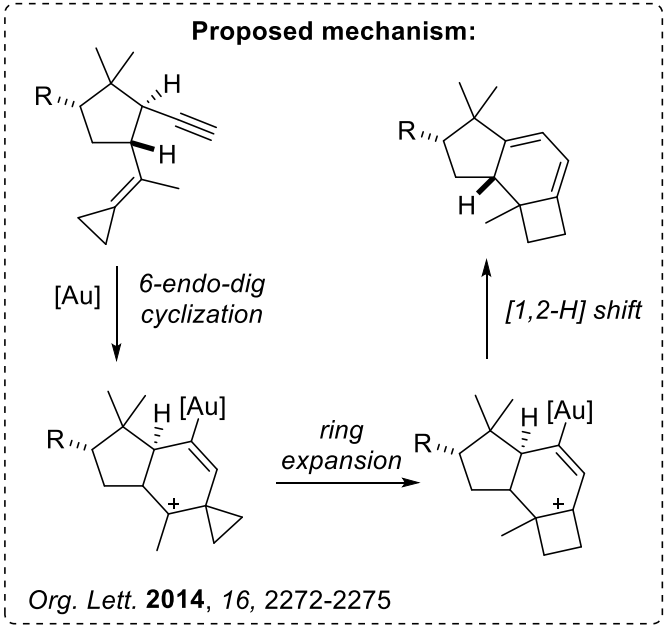


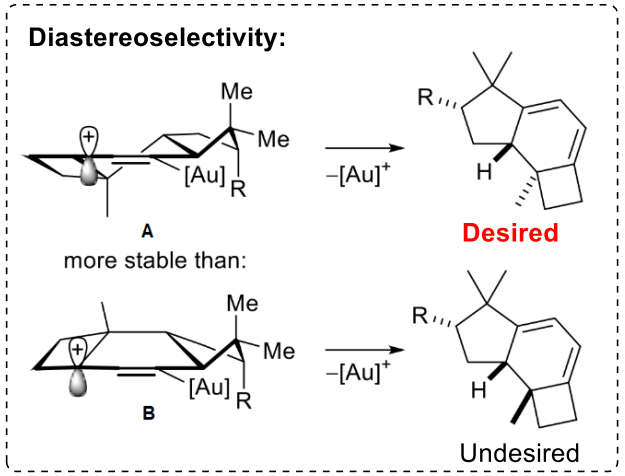
TPAP

Au-catalyzed cycloisomerization



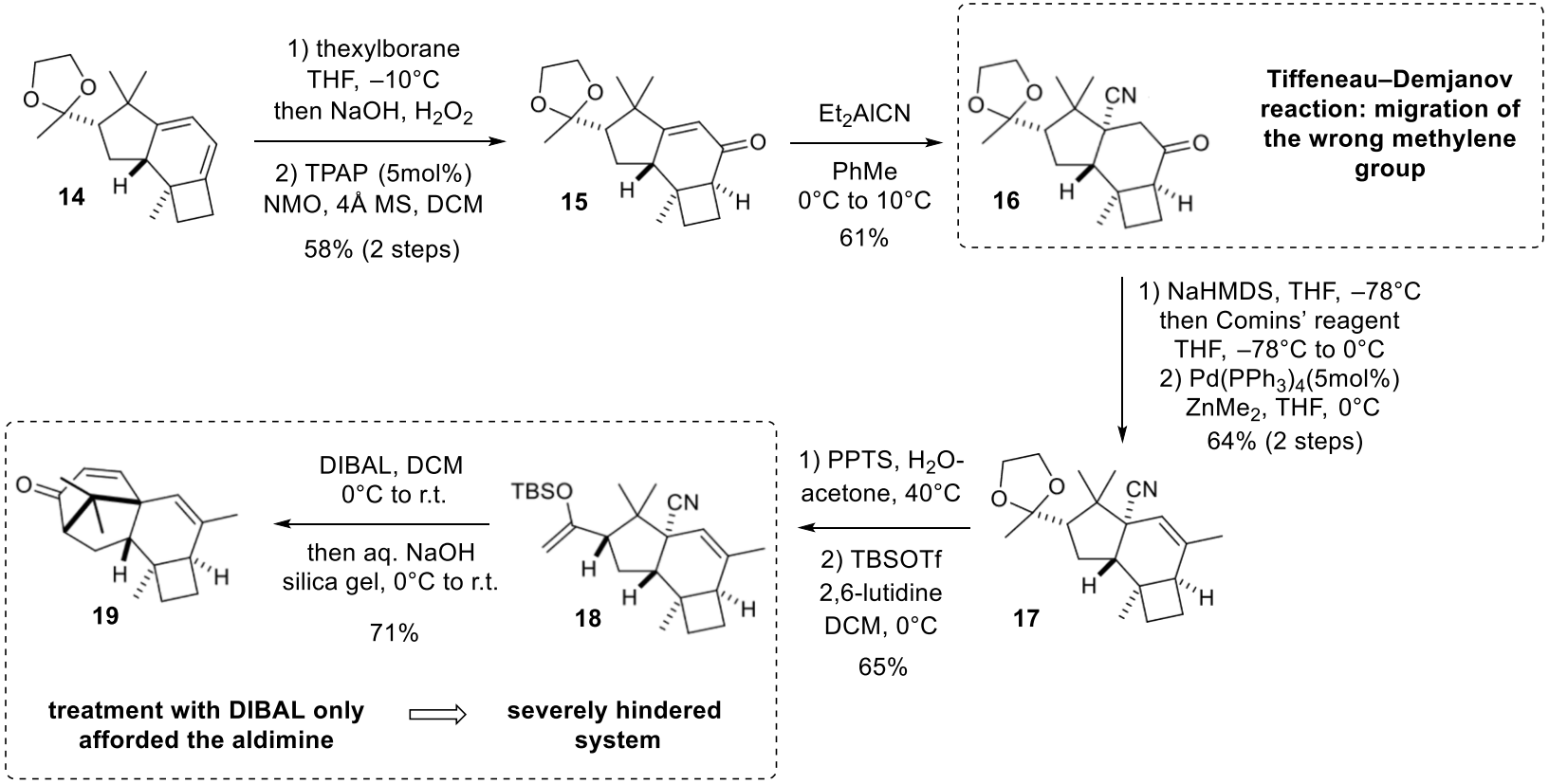




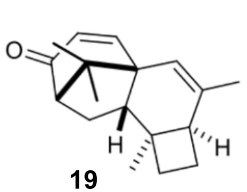


For regioselectivity of 5-*exo-dig vs* 6-*endo-dig*: *Org. Lett.* **2011**, *13*, 5580-5583

Introduction of bicyclo[3.2.1]octane ring



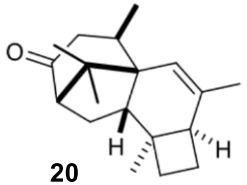
Key ring expansion



19

CuI, MeLi, $BF_3 \cdot OEt_2$
Et_2O, –78°C to 10°C

89%

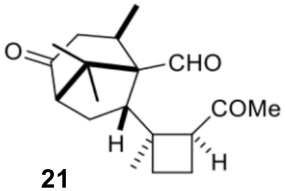


20

Structure secured by X-ray crystallography

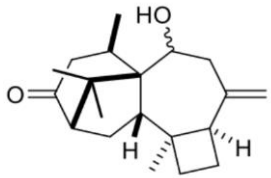
$RuCl_3 \cdot xH_2O$ (20mol%)
$NaIO_4$, DCE–H_2O (5:4)

65%;



21

1) LHMDS, THF
–78°C to 0°C
2) Ph_3PCH_3Br, KOt-Bu
THF, 0°C to r.t.
79% (2 steps)

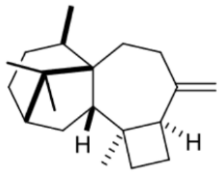


22

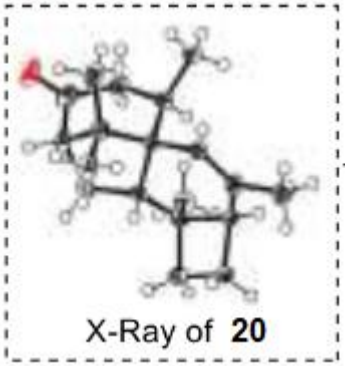
1) DIBAL, DCM, 0°C
2) KHMDS, CS_2, THF
–78°C to r.t., then MeI

3) AIBN (38mol%), Bu_3SnH
PhH, 80°C

75% (3 steps)

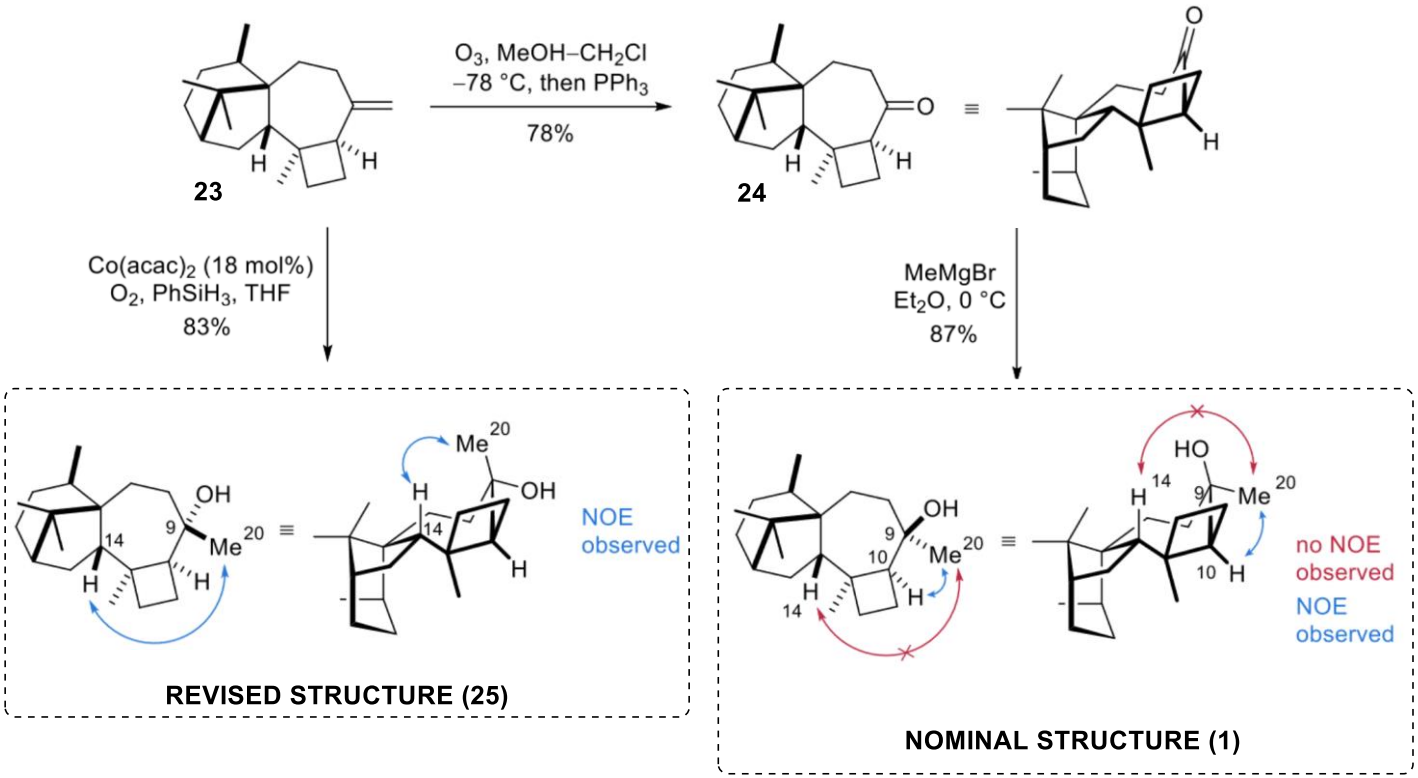


23



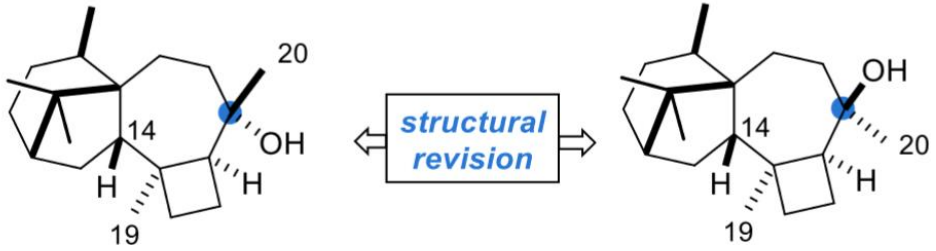
X-Ray of **20**

End game and stereochemical revision



To sum up:

- First total synthesis of nominal harziane diterpenoid **1**
- Reassigment of configuration of the natural product
- Key step - enyne cycloisomerization leading to a key quaternary stereocenter within a cyclobutane



Harziane diterpenoid (revised structure)

25

Harziane diterpenoid (nominal structure)

1