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A Journey into the Total Synthesis of Polycyclic Cytochalasines

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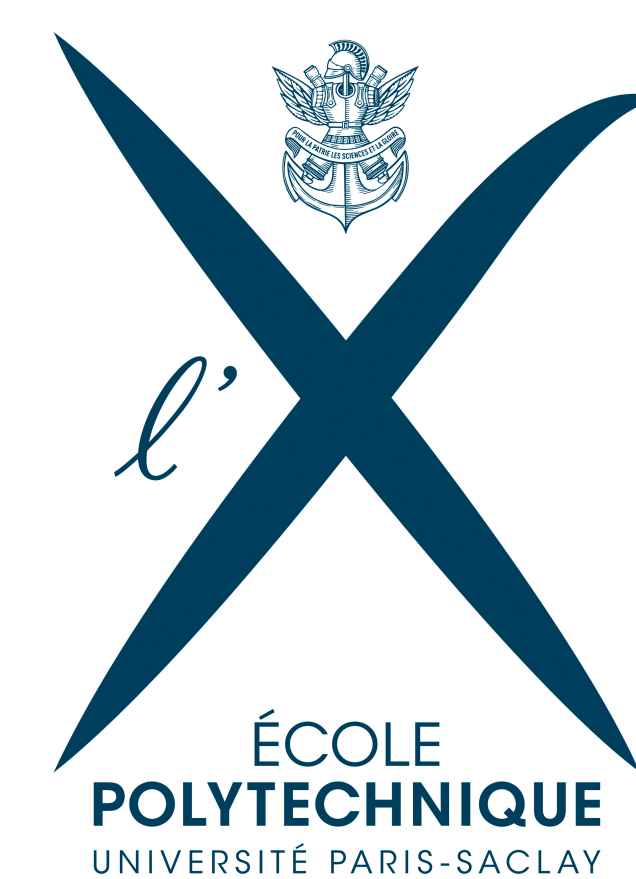
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A Journey into the Total Synthesis of Polycyclics Cytochalasines



Oscar Gayraud, Bastien Nay*

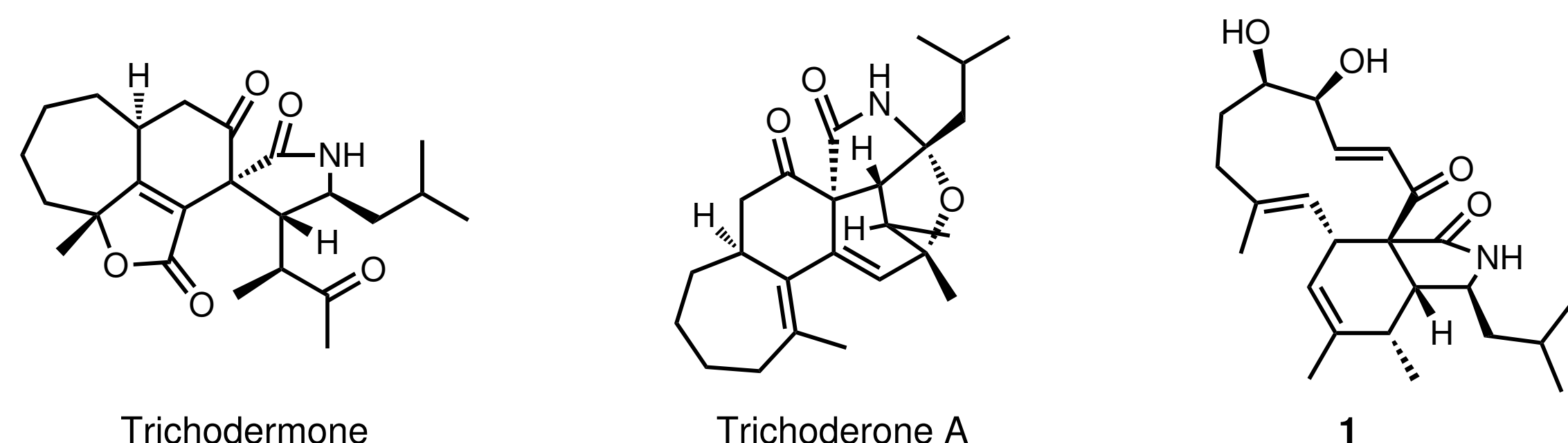
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1. Introduction

Trichoderme and Trichoderone A have been isolated from the endophytic fungus *Trichoderma gamsii*.^[1, 2] Unprecedented **7/6/6/5/5** and **7/5/6/5** polycyclics cores possibly arised from a common isolated intermediate (**1**).

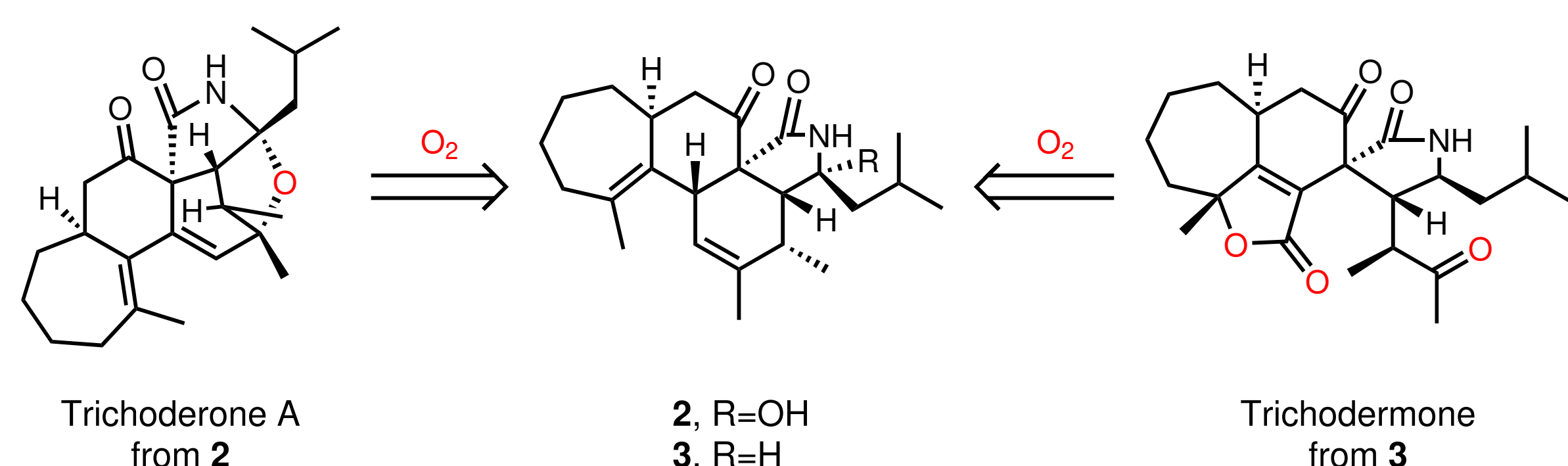


Panax Notoginseng

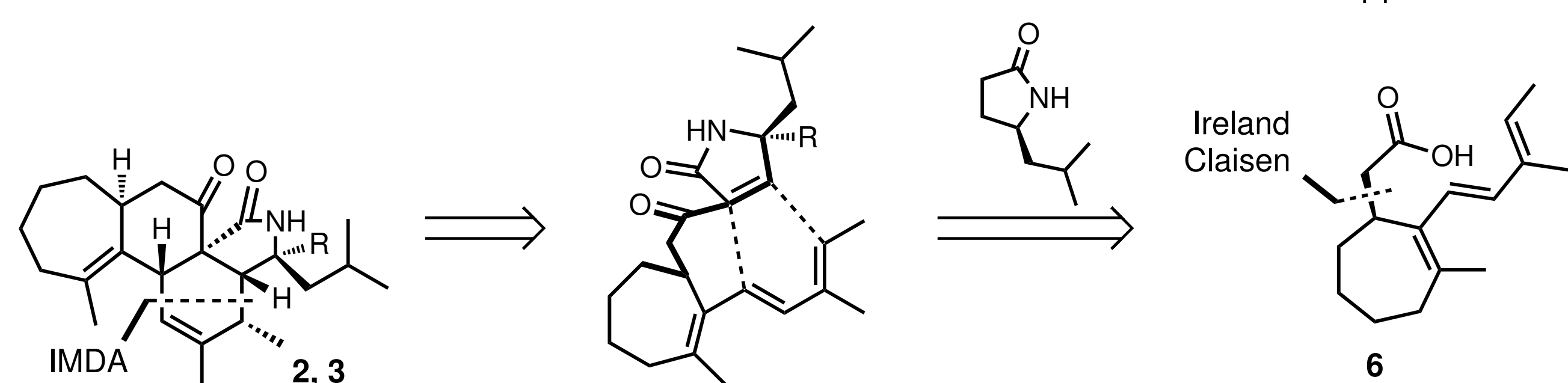
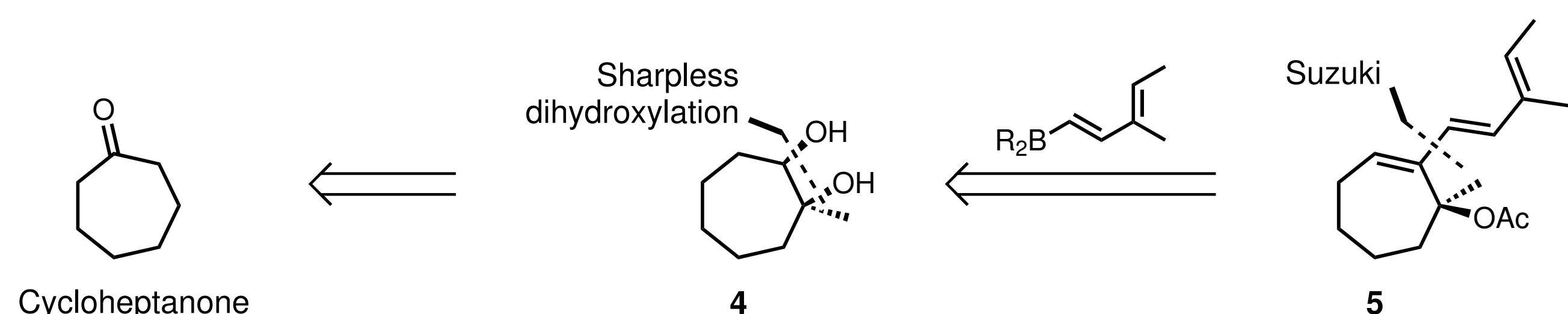


2. Retrosynthesis

Starting from key intermediates **2** and **3**, Trichoderone A and Trichoderme might be achieved through biomimetic late stage cyclization and oxidation.

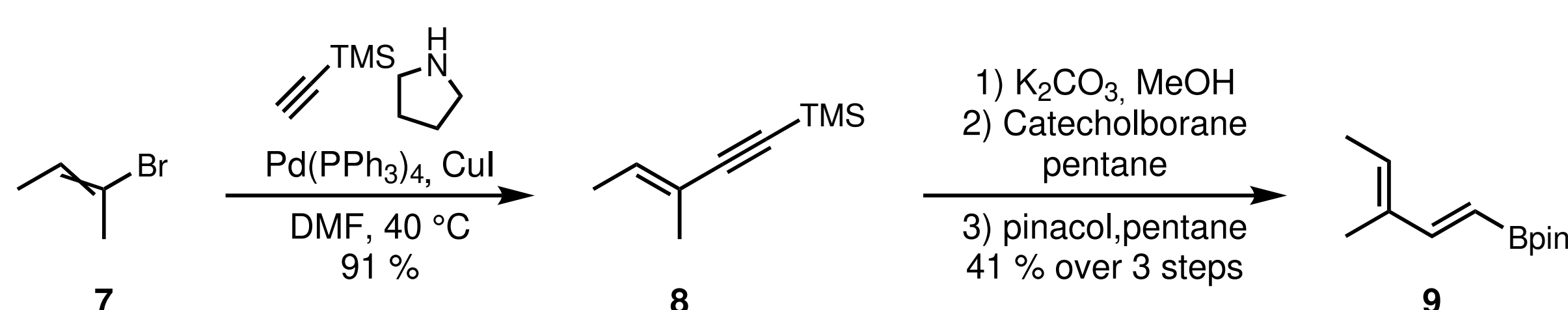


Cycloheptanone will be functionalized using oxidation, coupling and rearrangement reaction. Then an Intramolecular Diels-Alder (IMDA) reaction will allow access to the **7/6/6/5** core.

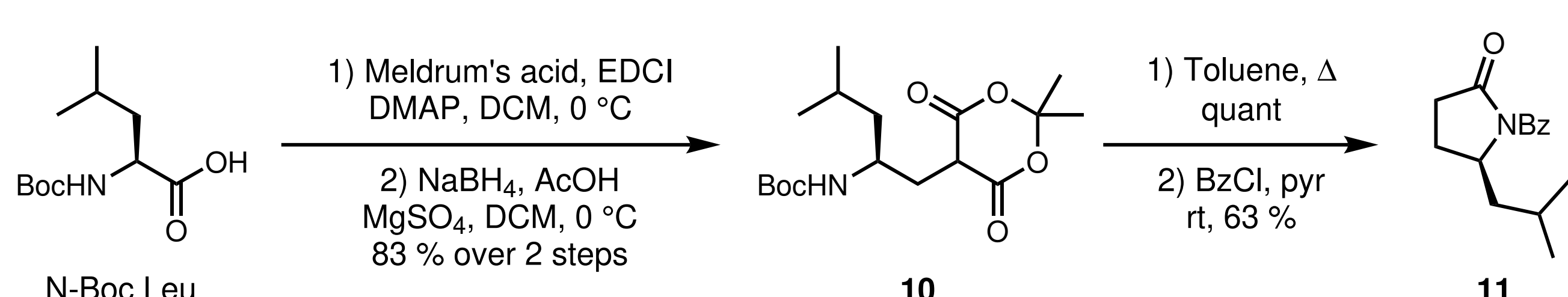


3. Synthesis of 9 and 11

Inspired by Lallemand's work,^[3] diene **9** has been synthesized through a Sonogashira coupling followed by a hydroboration of the alkyne.

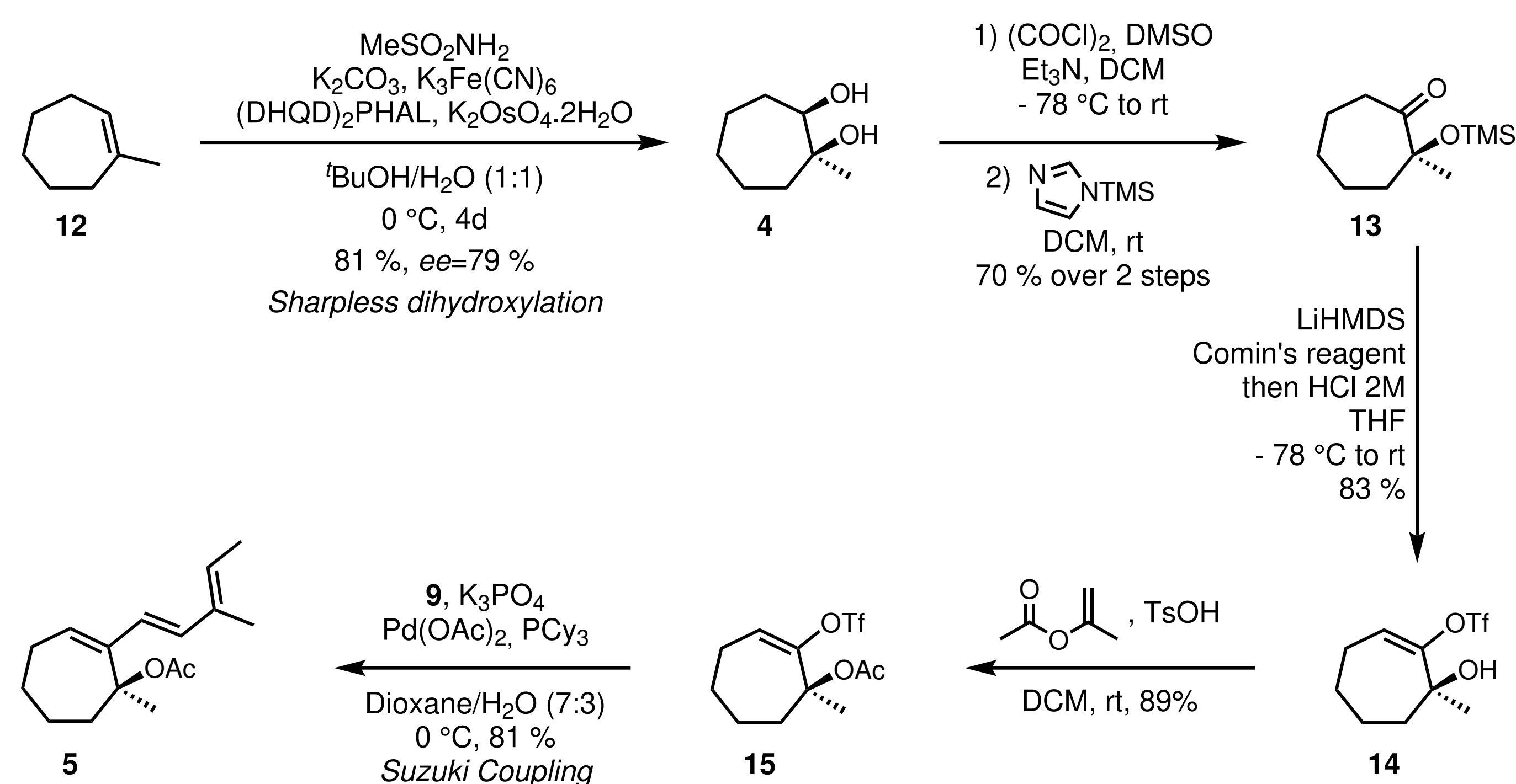


Lactame **11** has been access from the protected amino acid N-Boc Leucine through a sequence involving formation of a carbamate followed by a reduction then a cyclization and a protection.^[4]

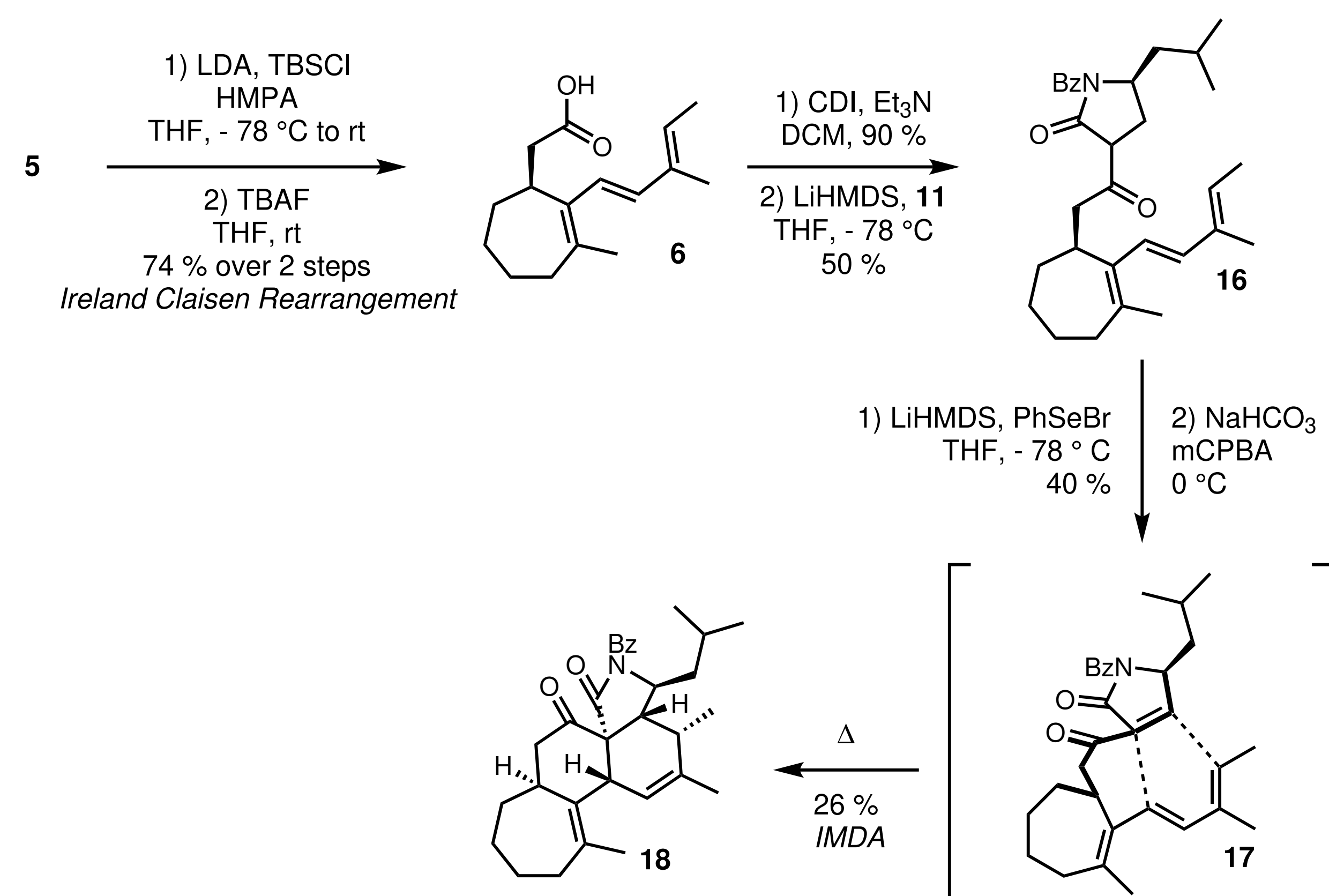


4. Synthesis of the key intermediate 18

Fully functionalized 7-membered ring **5** has been synthesized using Sharpless dihydroxylation and a Suzuki coupling.

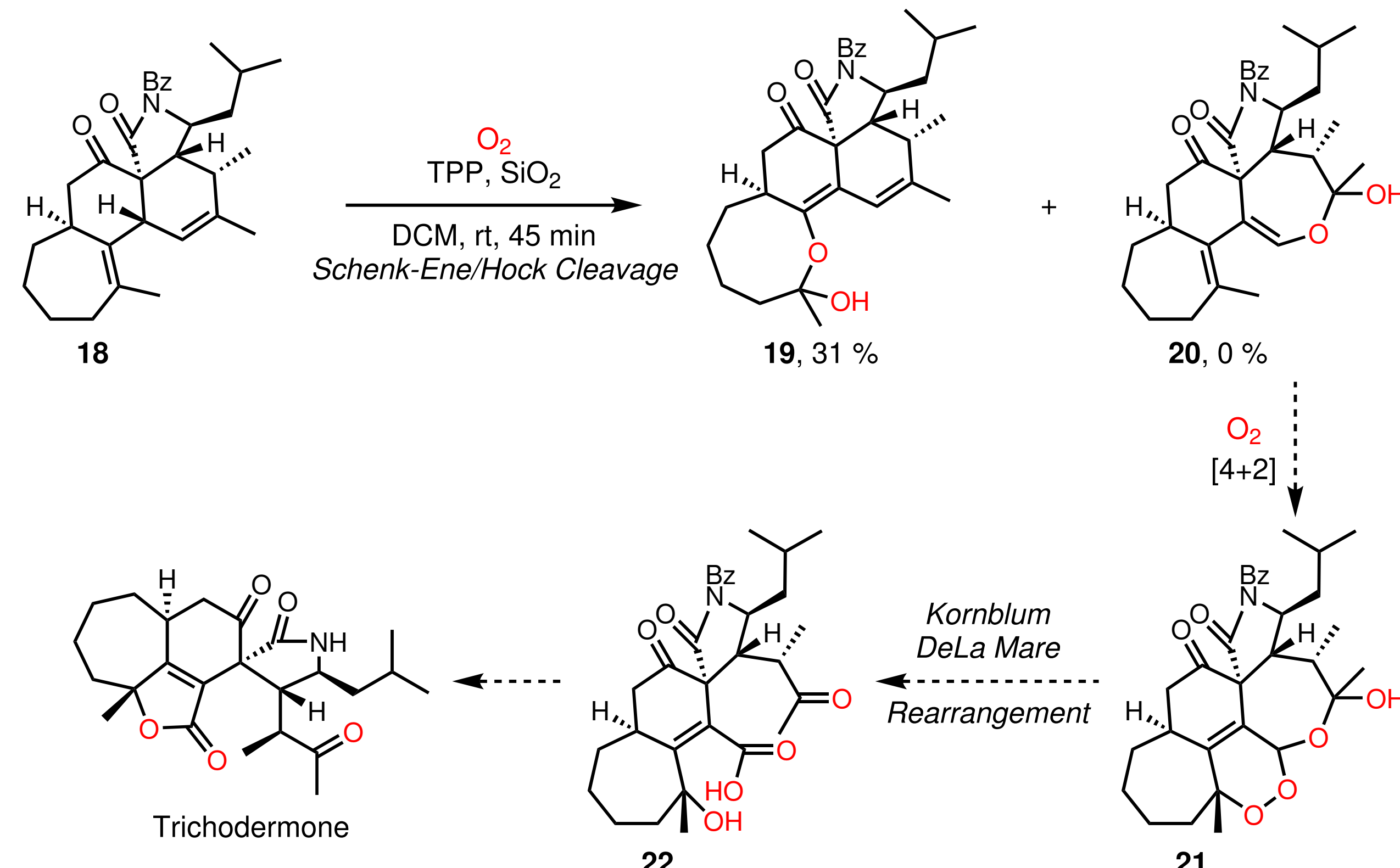


Protected key intermediates **18** has been access through an Ireland-Claisen rearrangement and an IMDA reaction enabled by the in situ generation of **17**.



5. Late Stage Oxidation

First try of the biomimetic late stage oxidation afforded the wrong regioisomer **19**. Work are in progress to access **20**.



References

- [1] Ding, G.; Wang, H.; Li, L.; Song, B.; Chen, H.; Zhang, H.; Liu, X.; Zou, Z. *J. Nat. Prod.* **2014**, *77*, 164-167.
- [2] Ding, G.; Wang, H.; Li, L.; Chen, A. J.; Chen, L.; Chen, H.; Zhang, H.; Liu, X.; Zou, Z. *Eur. J. Org. Chem.* **2012**, *13*, 2516-2519.
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- [4] Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867-12874.