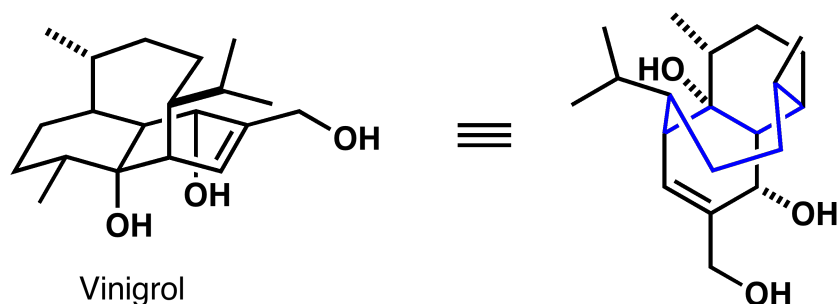


Climbing Mt. Vinigrol



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- Isolated from a fungus strain *Virgaria Nigra*, in Japan
- PAF antagonist IC₅₀=17 nM (epinephrine)
- TNF antagonist, 100% inhibition at 2.1 nM (HL60 cells)
- 2 total syntheses (Baran (2009), Barriault (2012)), 21 publications (approaches) and 8 Ph. D. dissertations

Isolation: Hashimoto M. et al, *J. Org. Chem.* **1987**, 52, 5292.

For a review: Barriault, L.; Tessier, G. *Org. Prep. Proc. Int.* **2007**, 39, 311

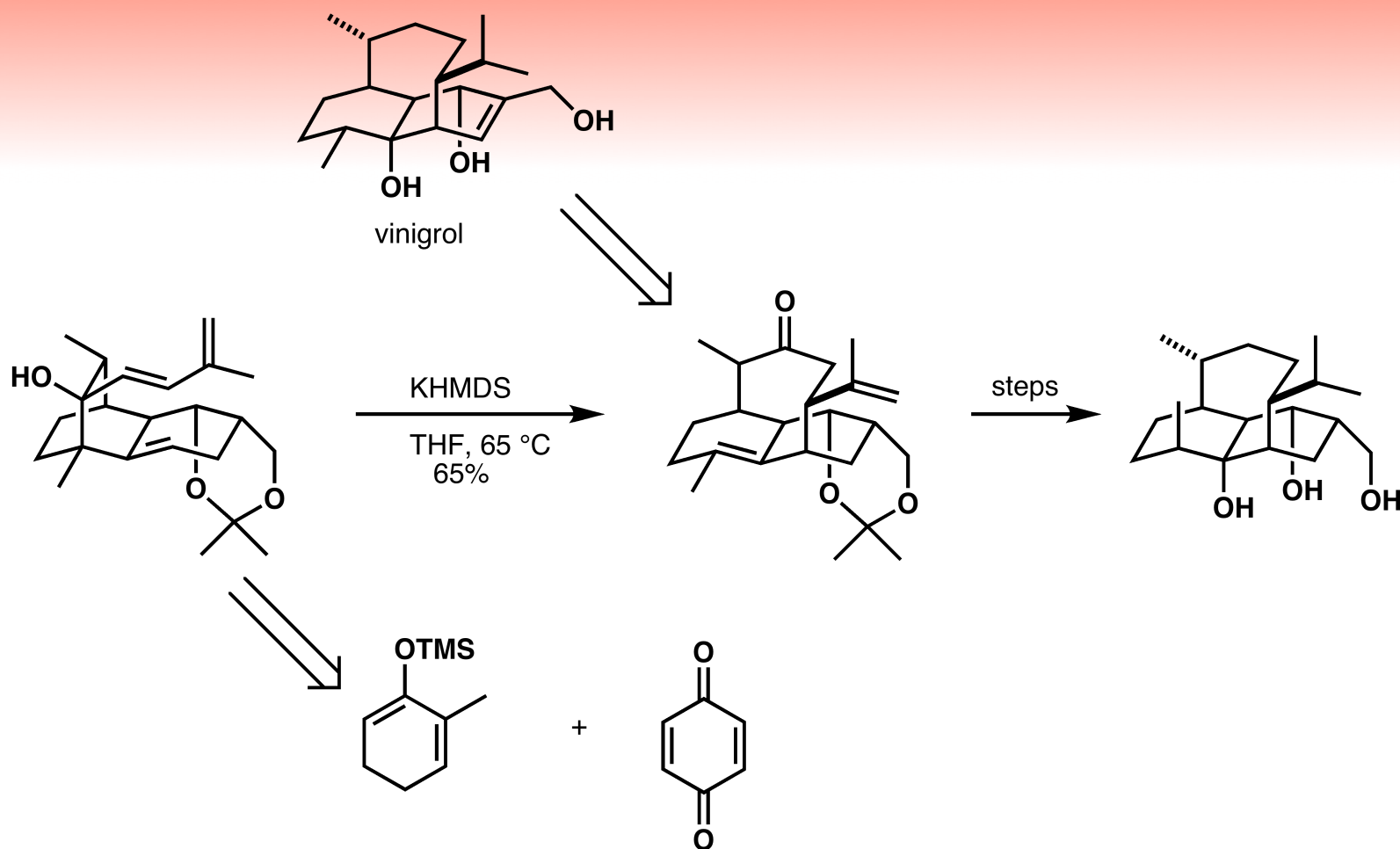
“The Conquest of Vinigrol: Creativity, Frustration and Hope »

Approach by Hanna (France)



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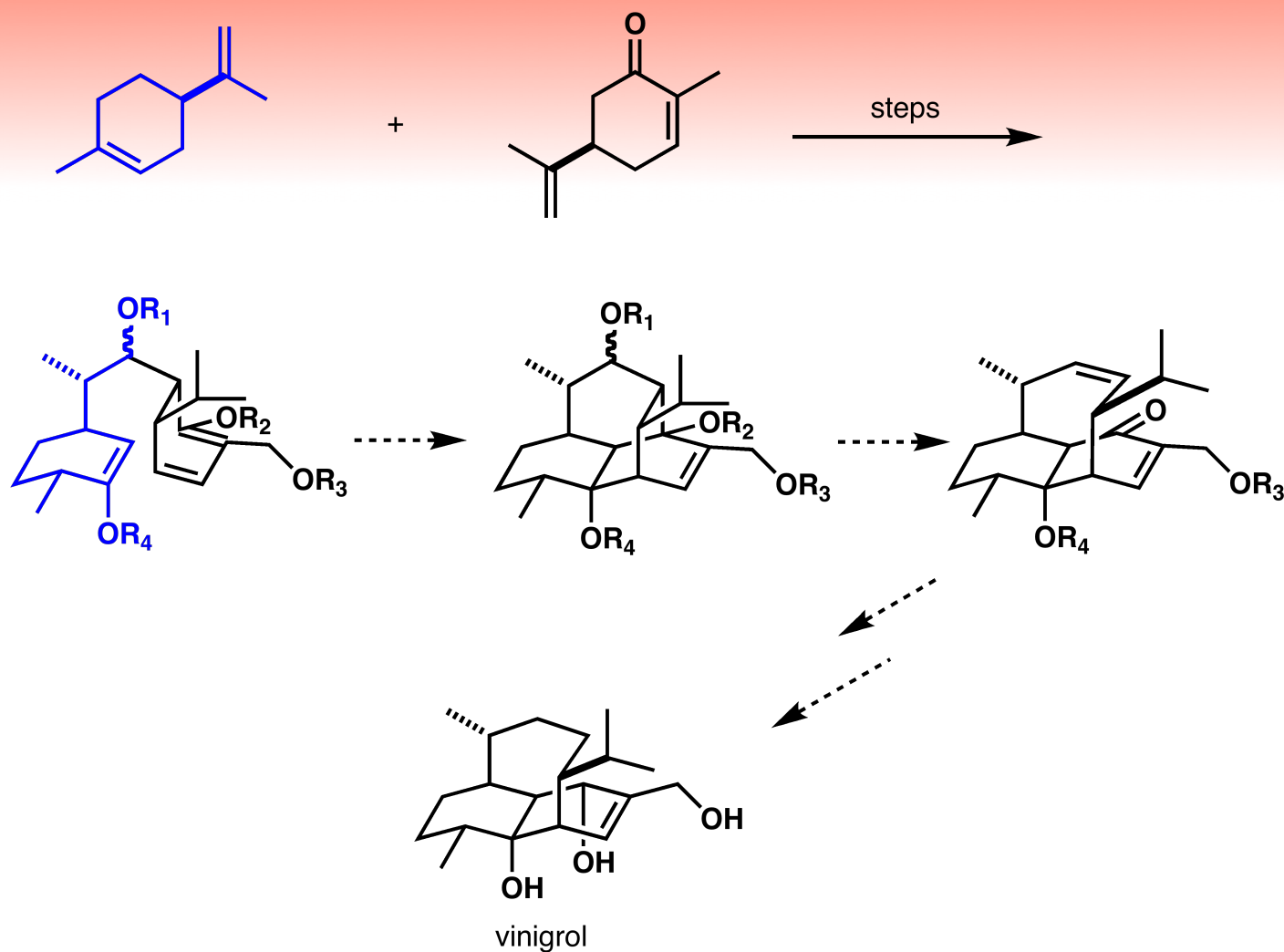
1) Hanna, I. et al. *J. Org. Chem.* **1993**, 58, 2349. 2) Hanna, I. et al. *Org. Lett.* **2003**, 5, 1139. 3) Hanna, I. et al. *J. Org. Chem.* **2009**, 74, 9337.

Approach by Corey (USA)



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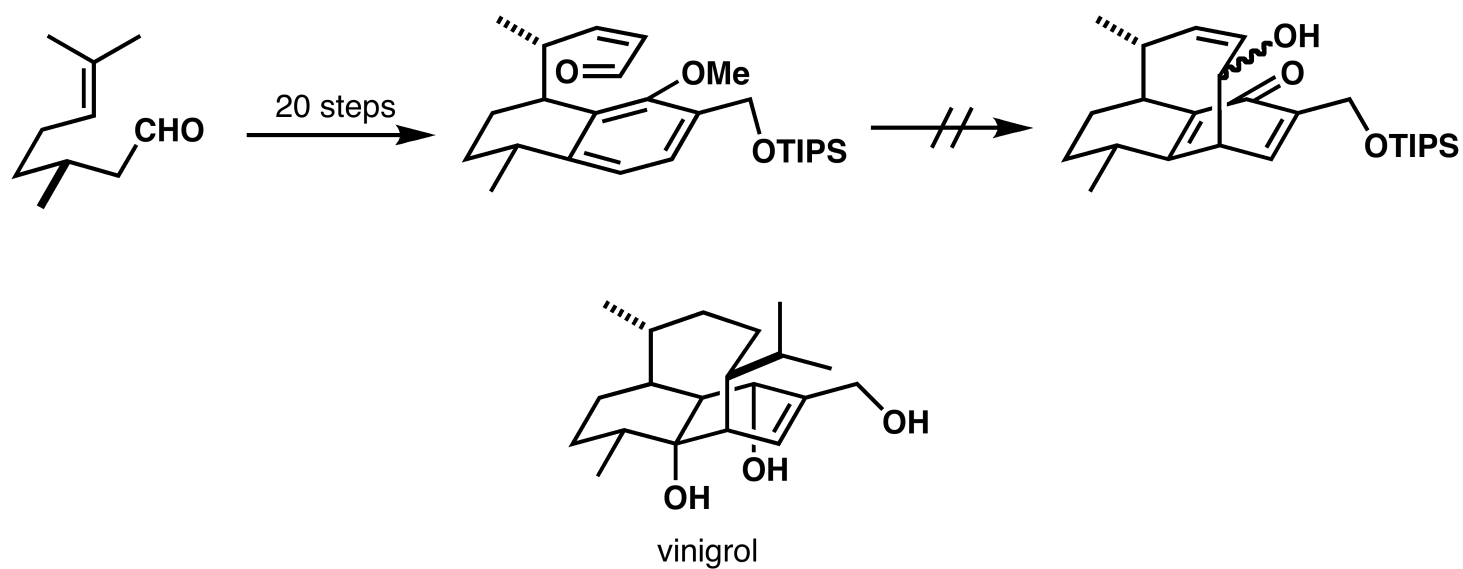
Corey and Goodman, Ph. D. thesis 2000

Approach by Corey (USA)



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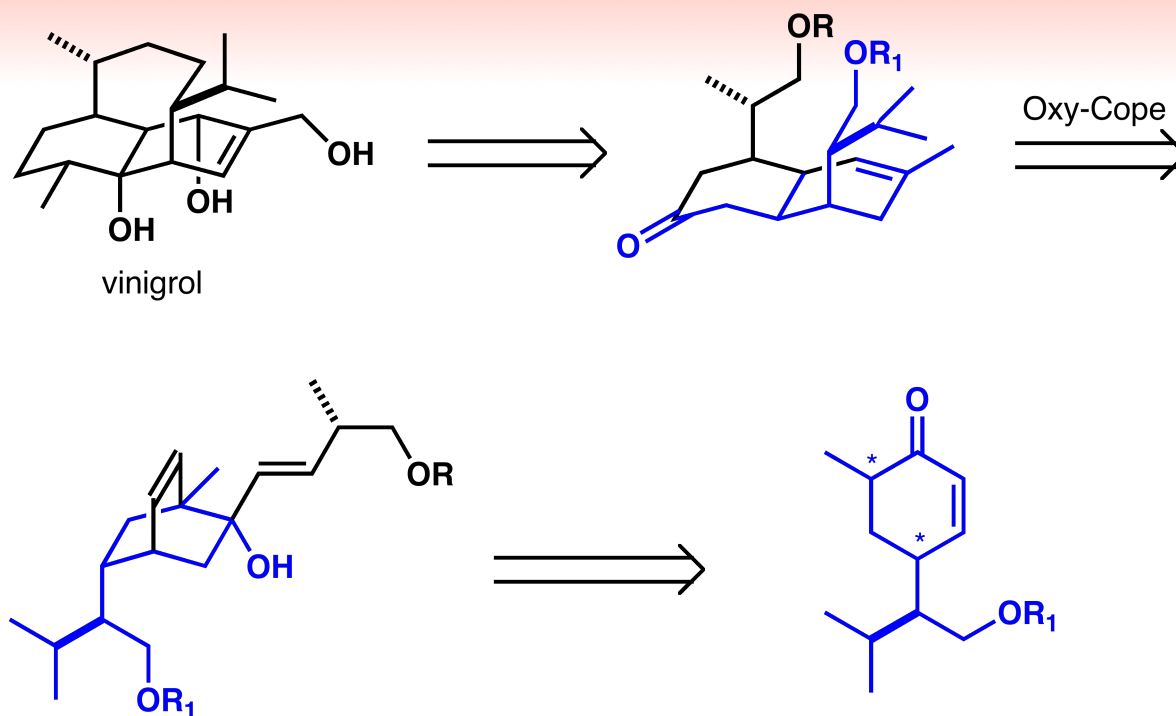
Corey and Palani, unpublished results

Approach by Paquette (USA)



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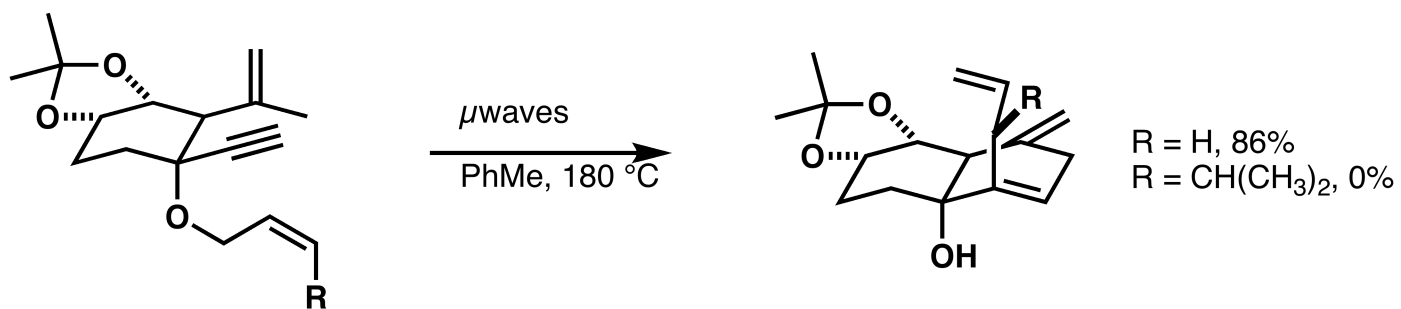
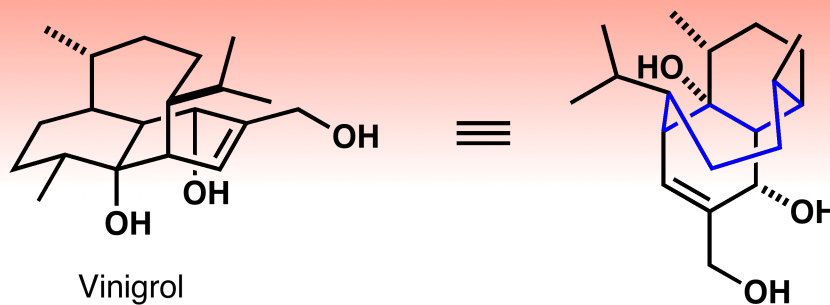
Paquette, L. A. et al. *J. Org. Chem.* **2003**, 68, 6096. 2) Paquette, L. A. et al. *J. Org. Chem.* **2005**, 70, 510. 3) Paquette, L. A. et al. *J. Org. Chem.* **2005**, 70, 514.

Approaches



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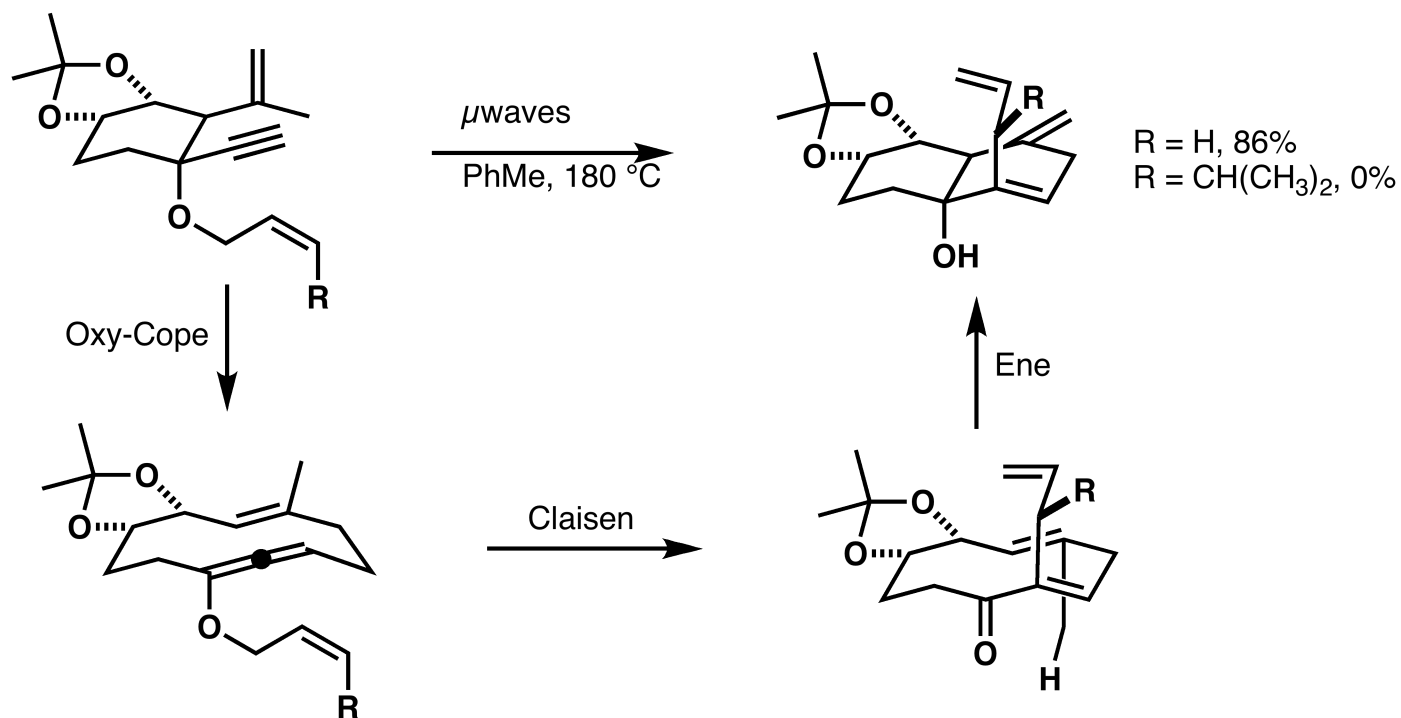
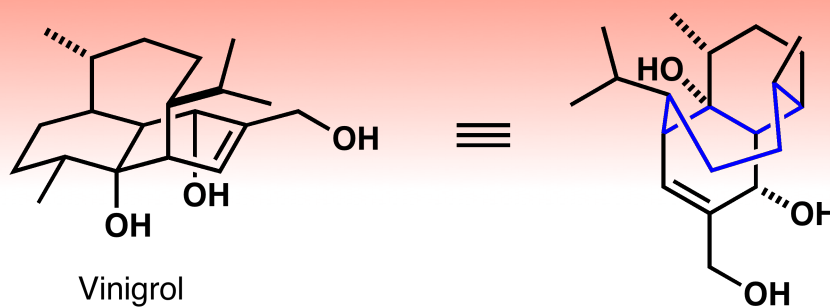


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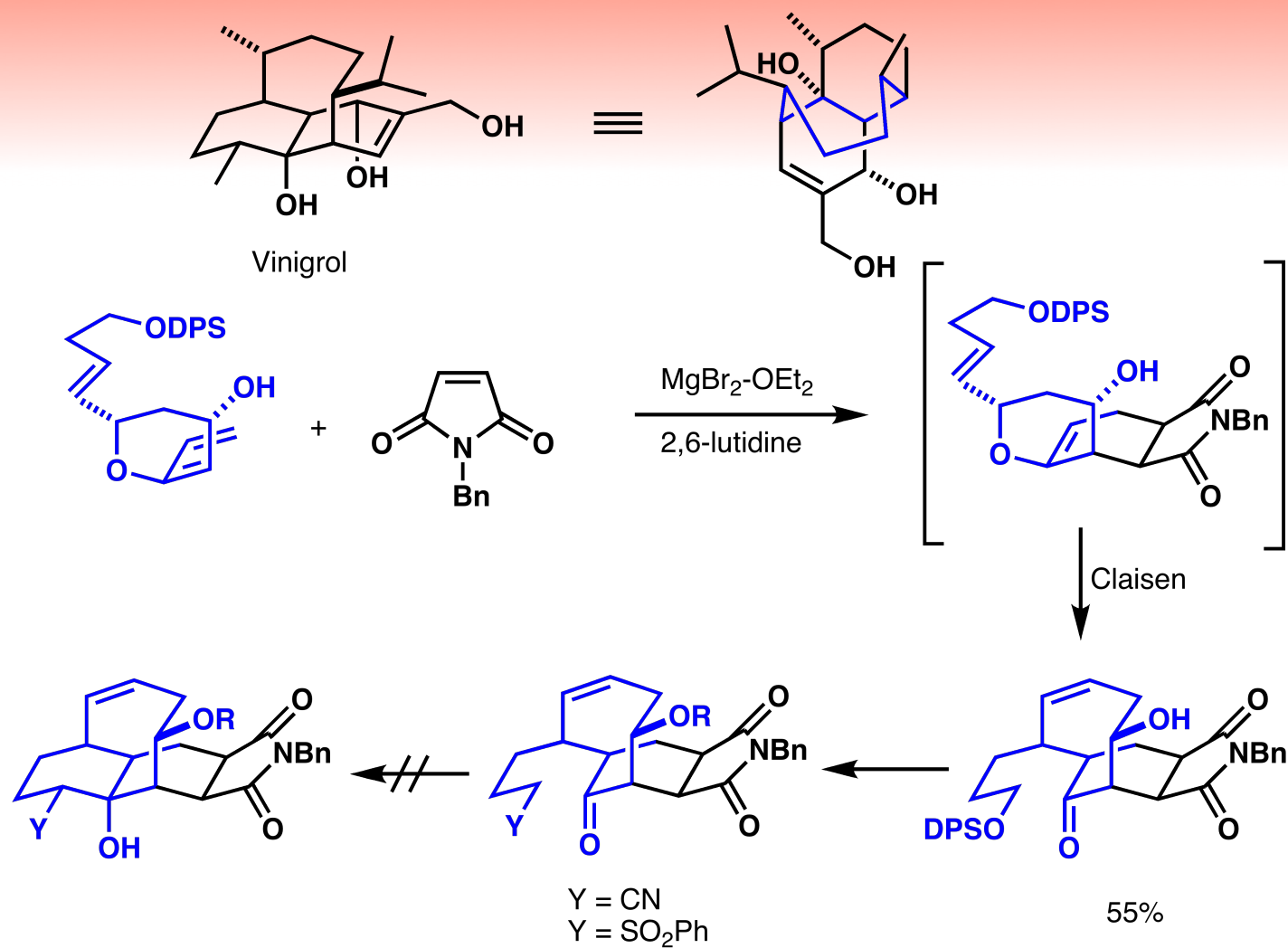
Morency, L; Barriault, L. *Tetrahedron Lett.* **2004**, 45, 6105

Approaches



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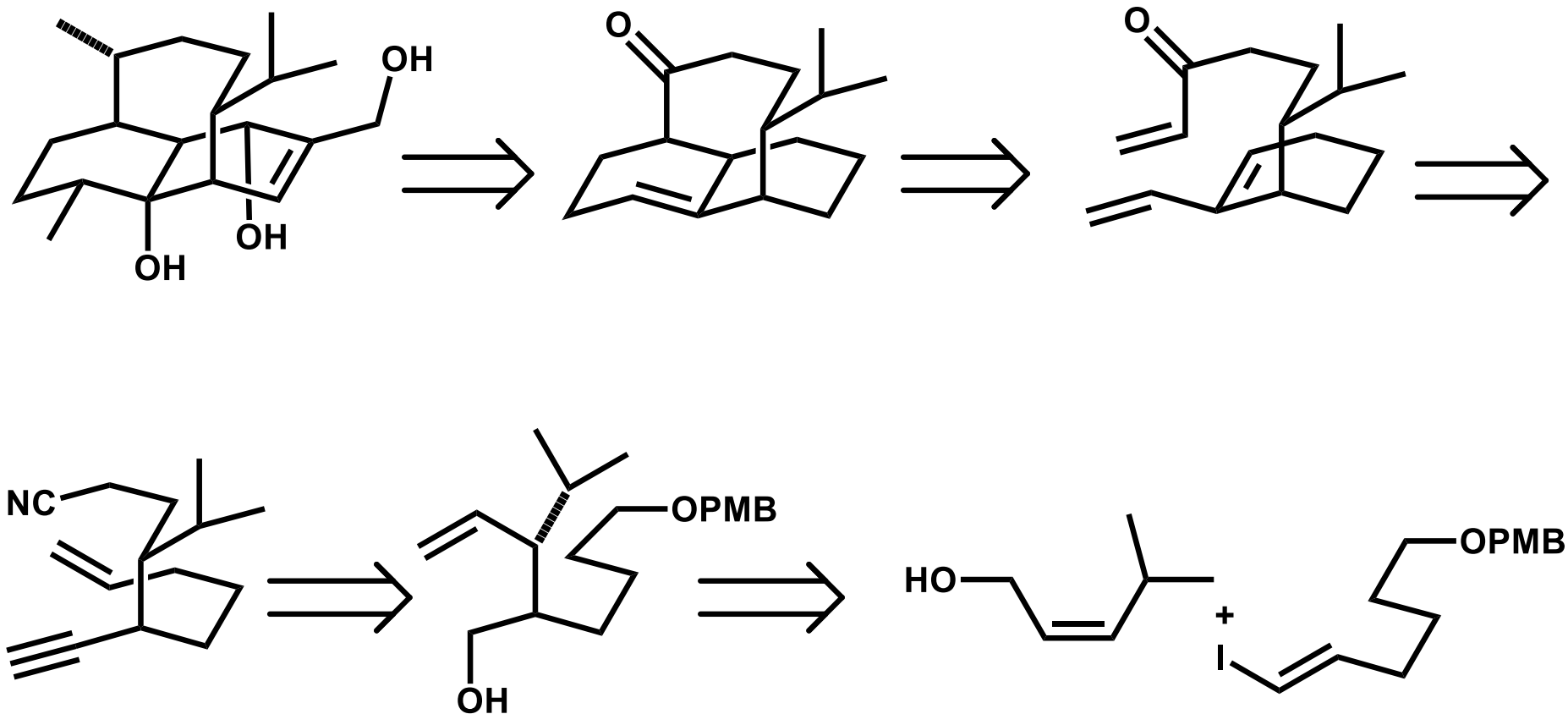


First Approach (Exploration Study)



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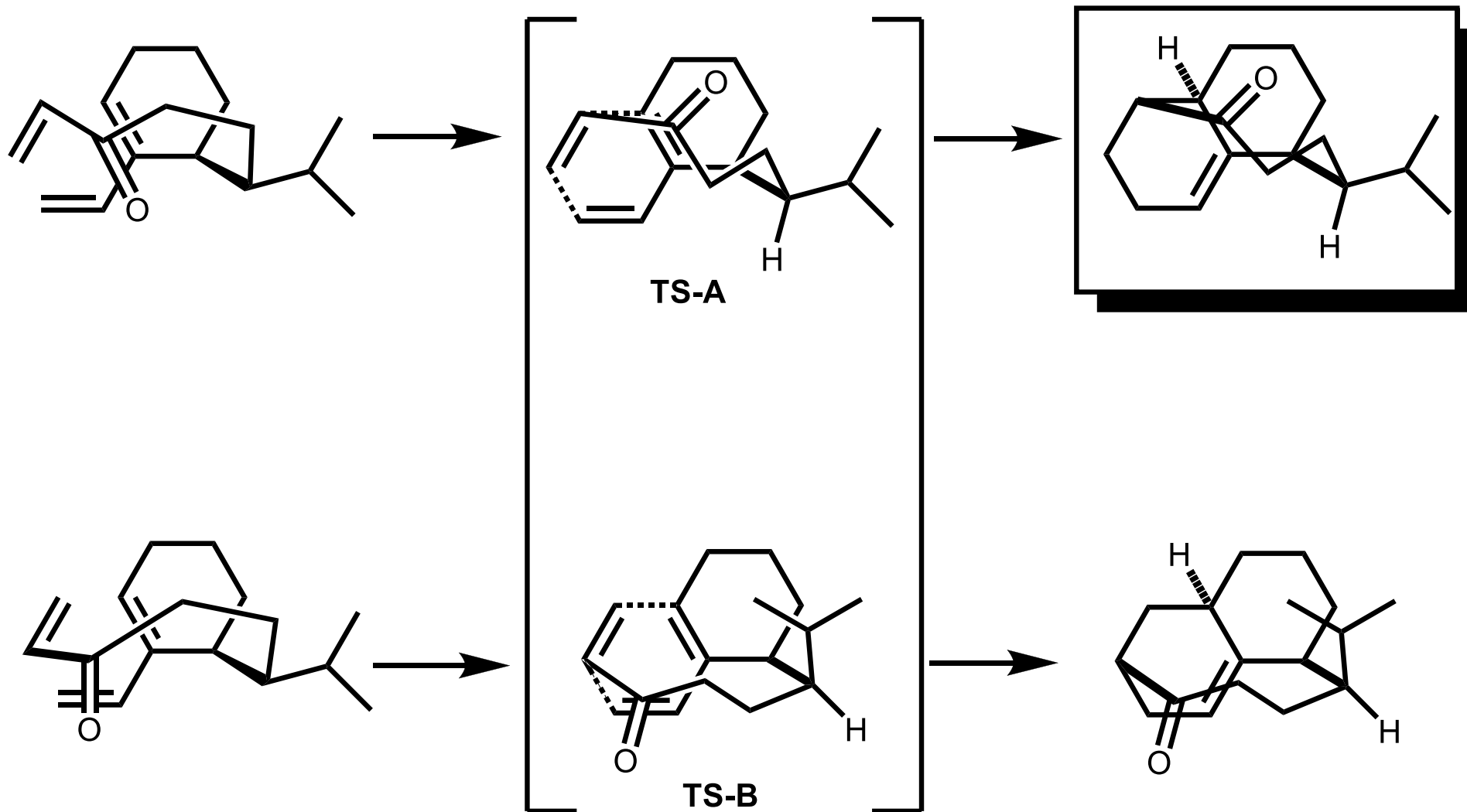


Diels-Alder Reaction



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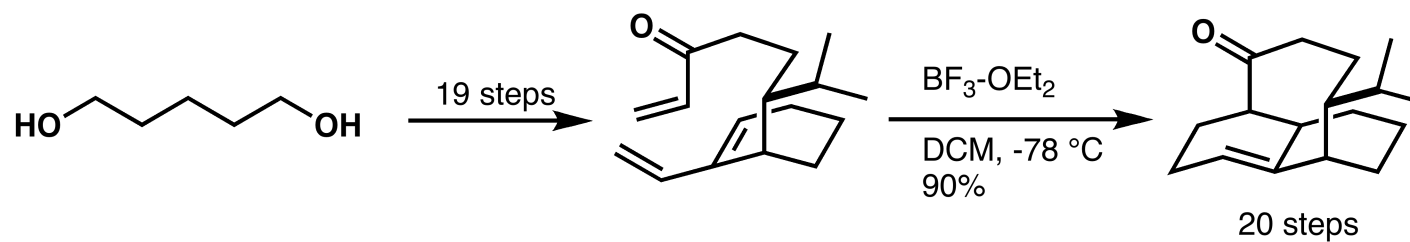
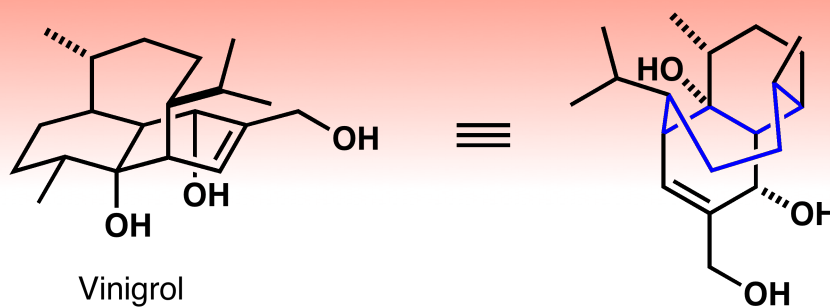


Approaches



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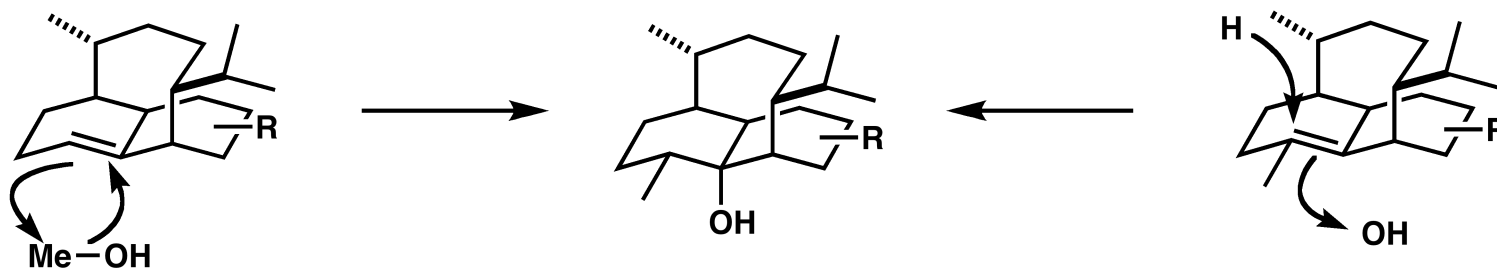
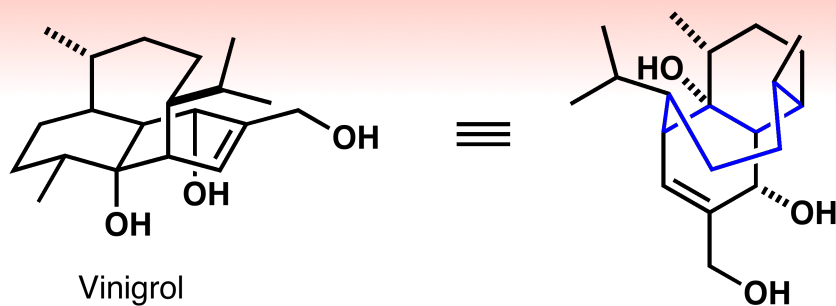
Barriault, L.; Grisé, C. M.; Tessier, G. *Org. Lett.* **2007**, 9, 1545

Most Difficult Challenge



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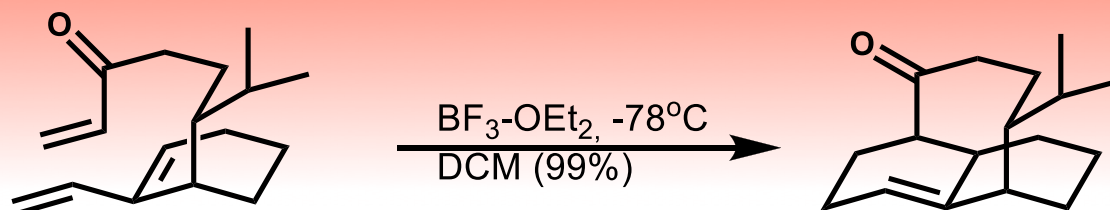


Other Approaches

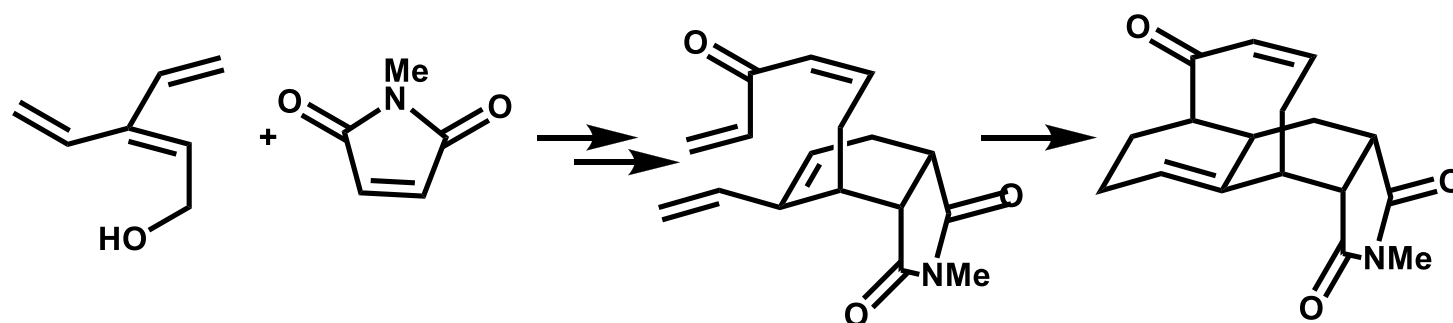


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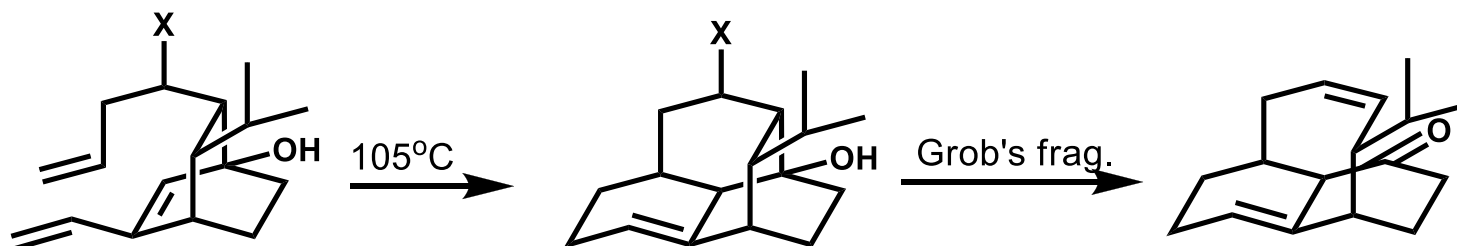
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Grisé, C.; Tessier, G.; Barriault, L. *Org. Lett.* **2007**, 9, 1545



Fallis, A. G.; Souewha, M. *Org. Lett.* **2007**, 9, 5163



Baran, P. S. et al *ACIEE* **2008**, 47, 3054

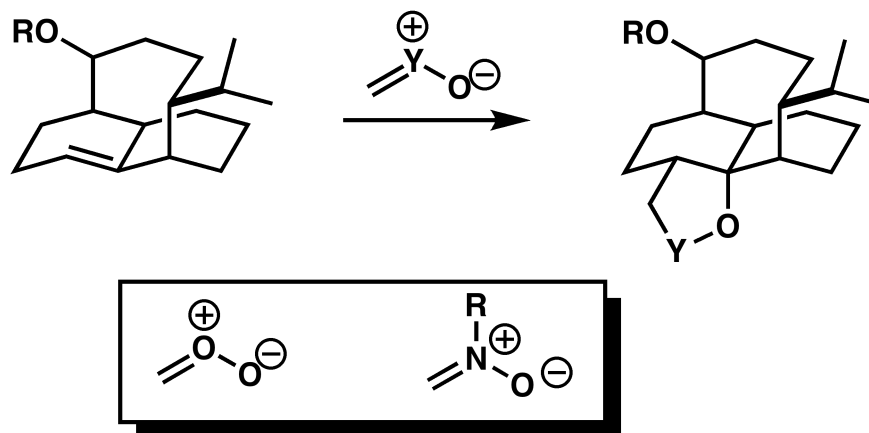
Most Difficult Challenge



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In 2007



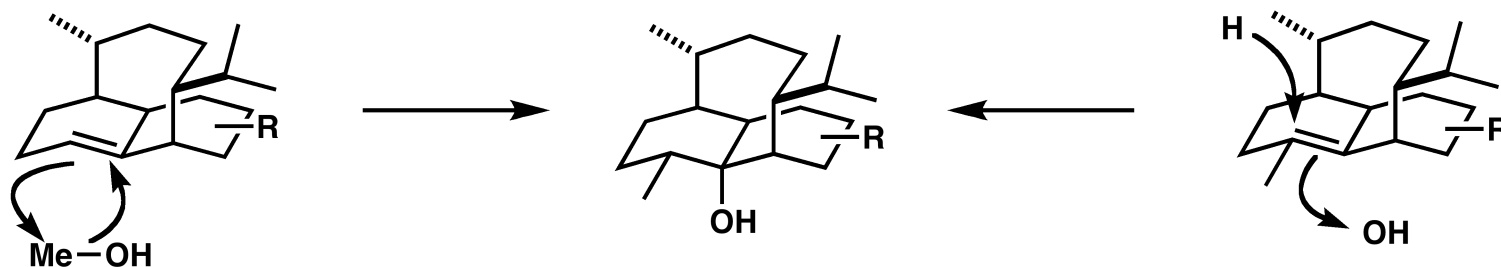
Christiane Grisé

Most Difficult Challenge



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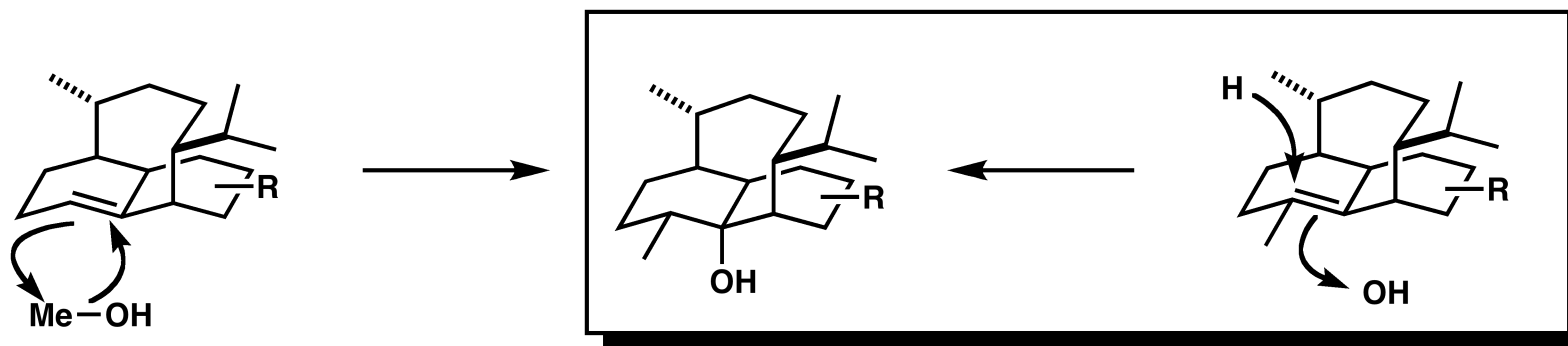
Christiane Grisé

Most Difficult Challenge



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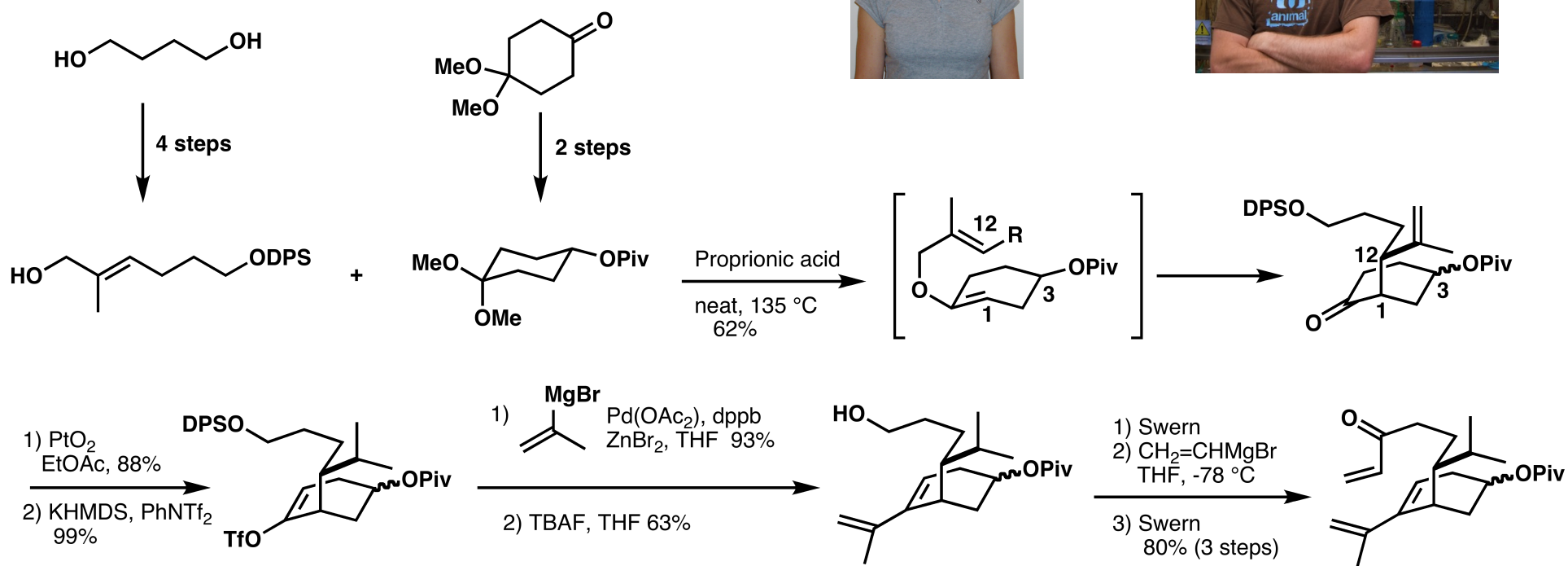
Christiane Grisé

Synthesis



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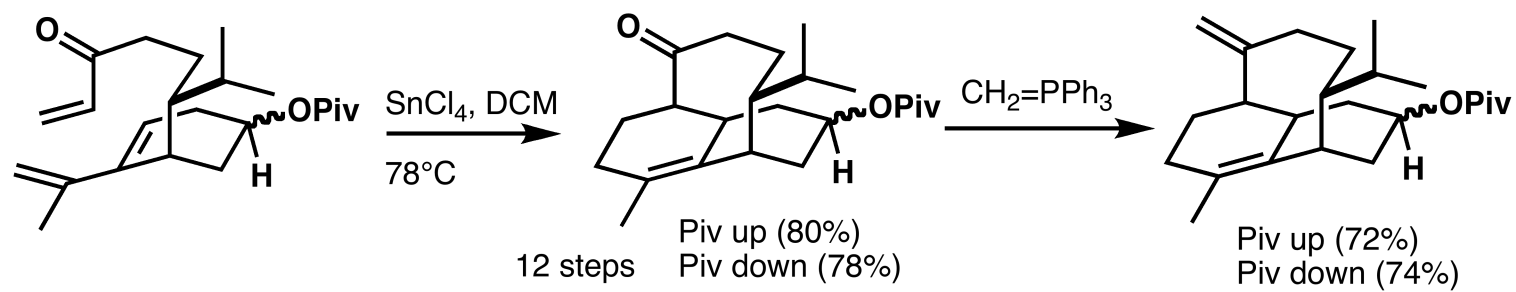
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Synthesis



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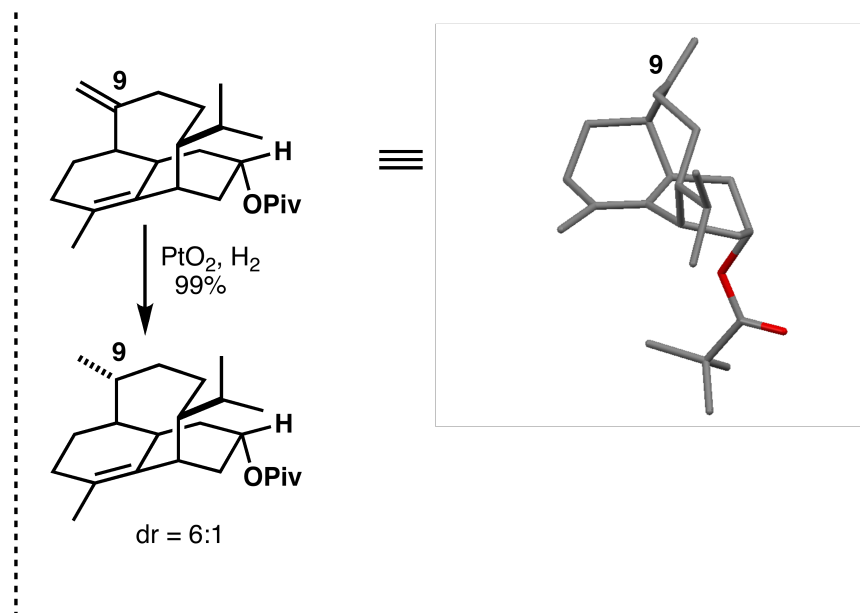
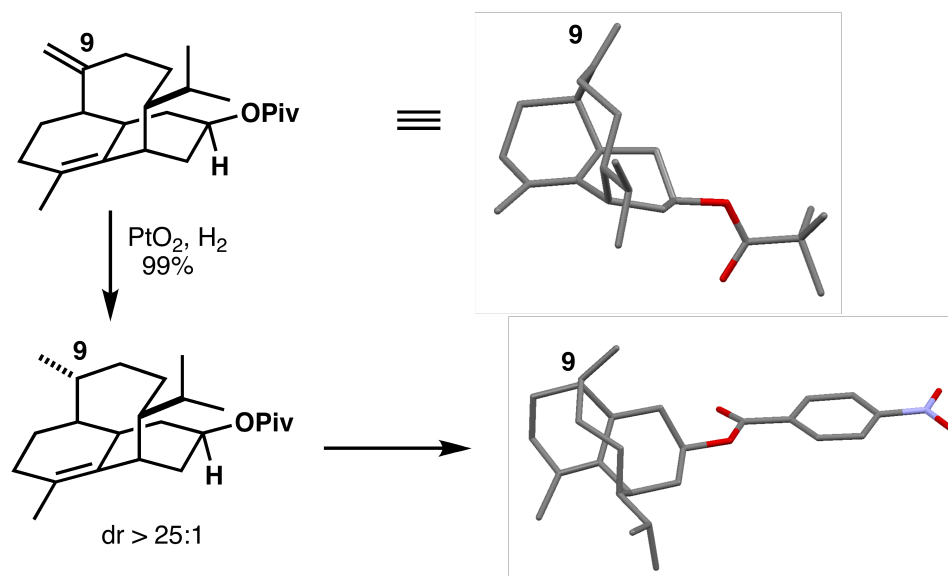
Critical hydrogenation



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End of 2007



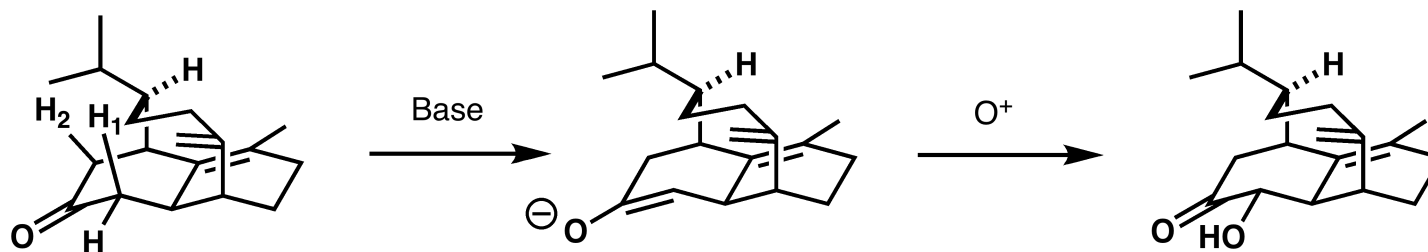
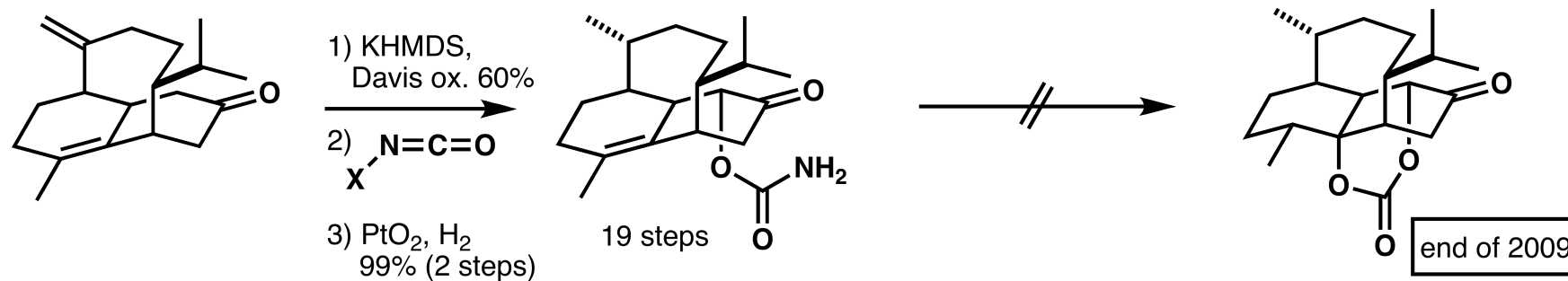
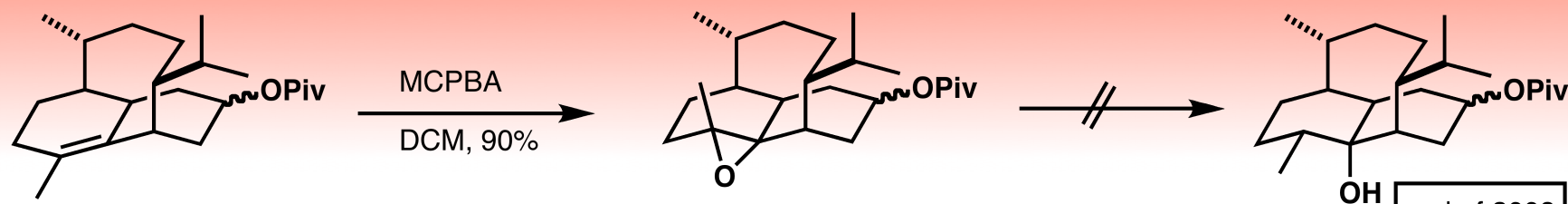
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Synthesis



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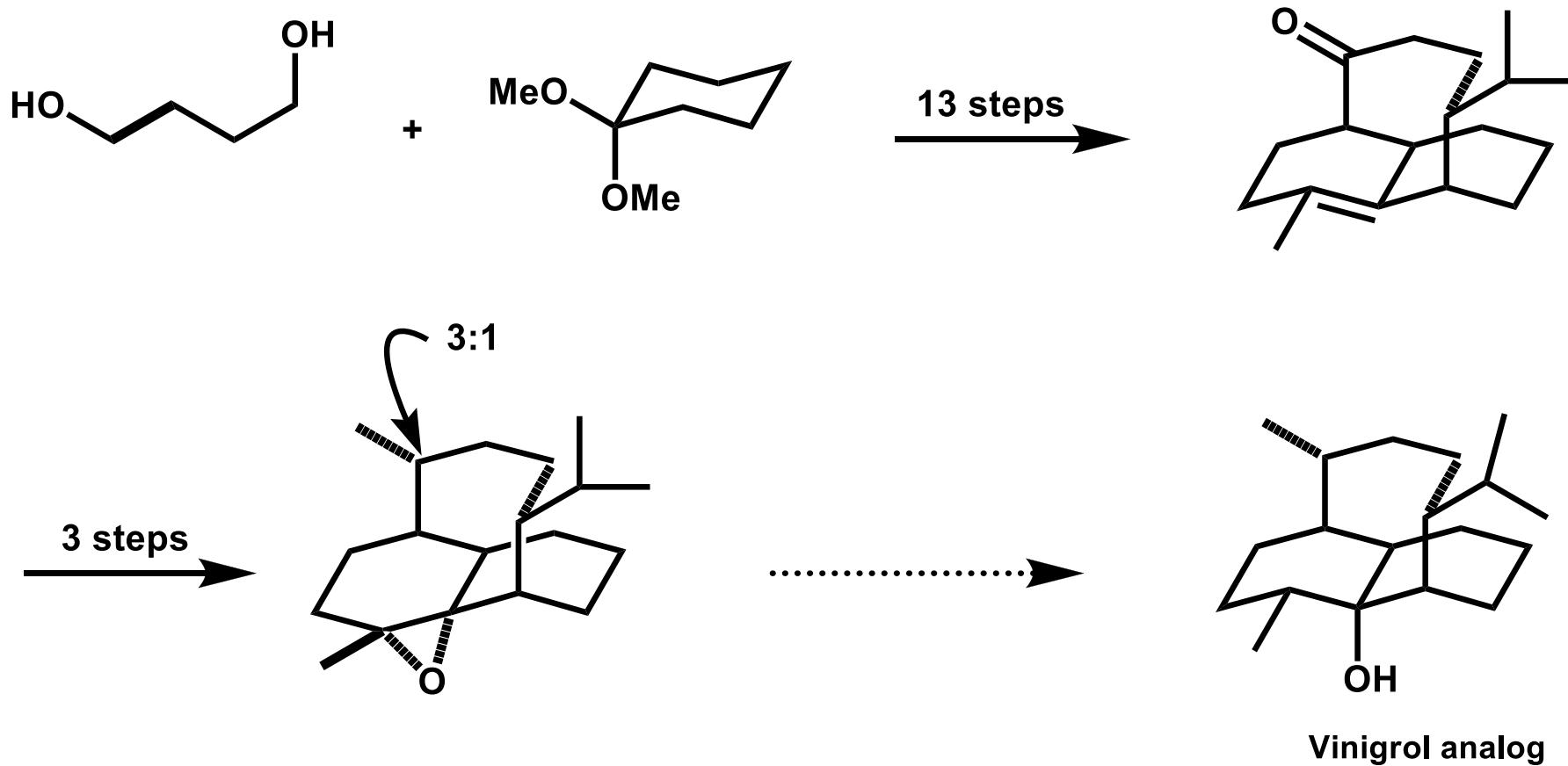
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Second Generation



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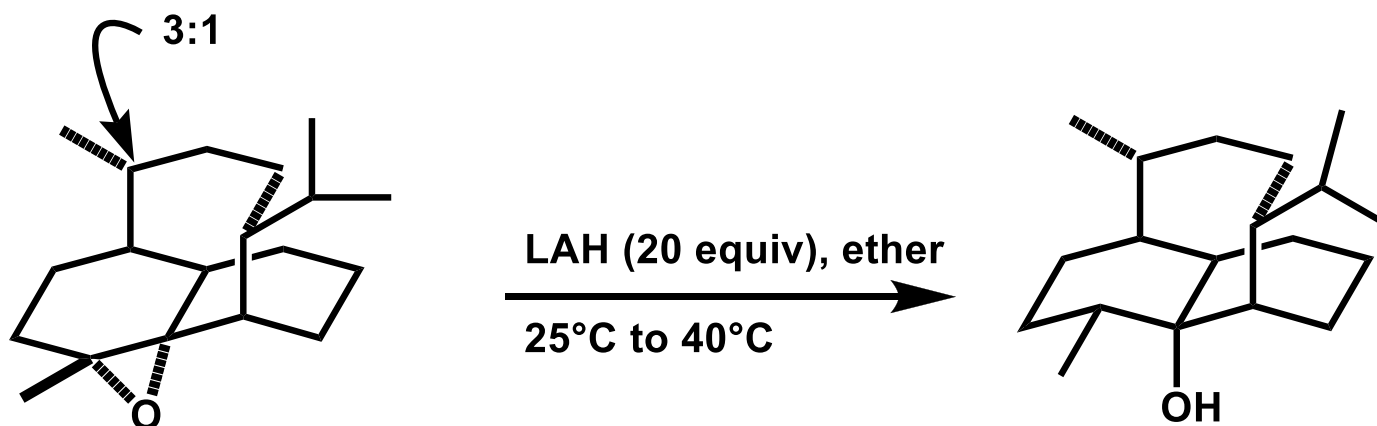
Christiane Grisé and Patrick Levesque

Epoxide Opening



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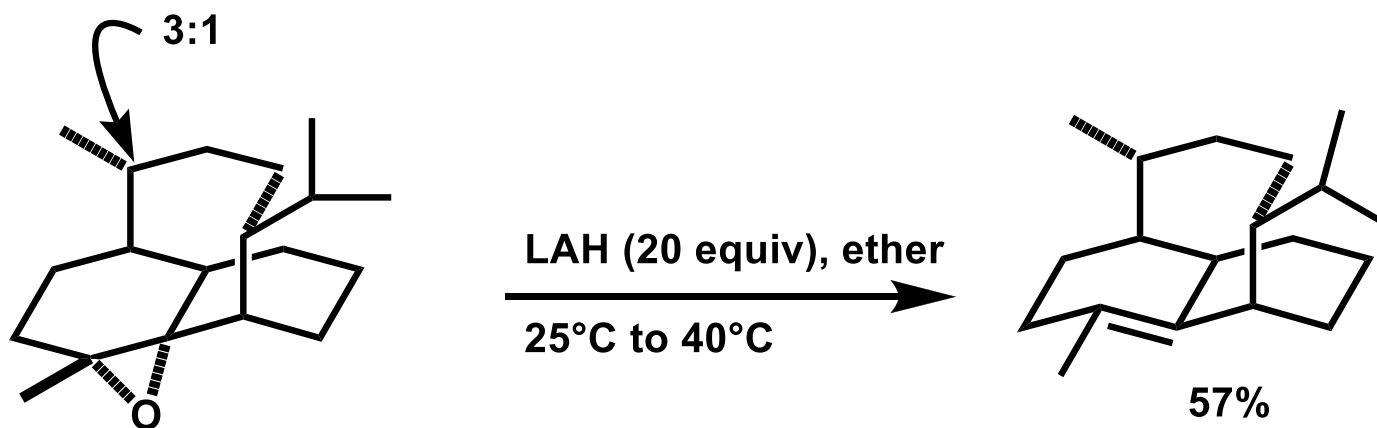
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Epoxide Opening



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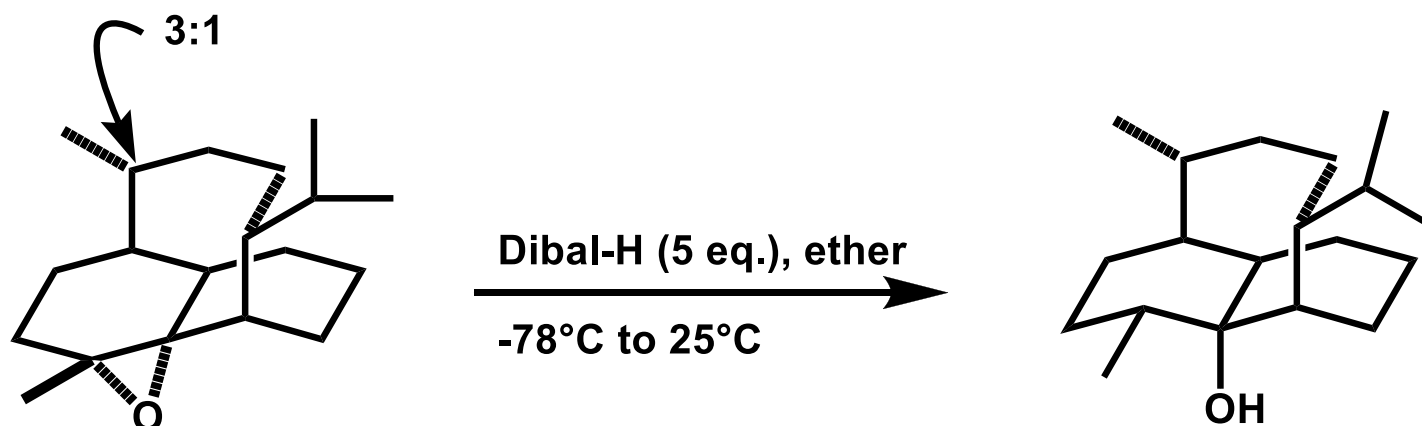
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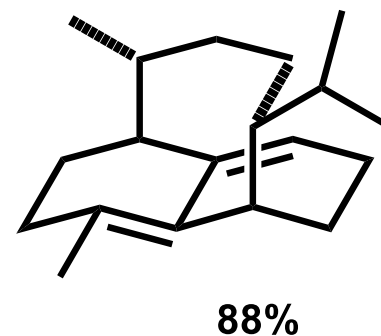
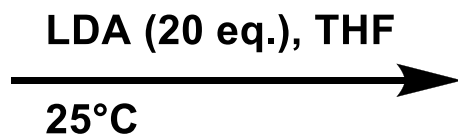
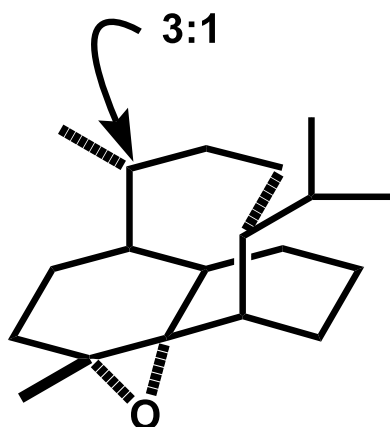
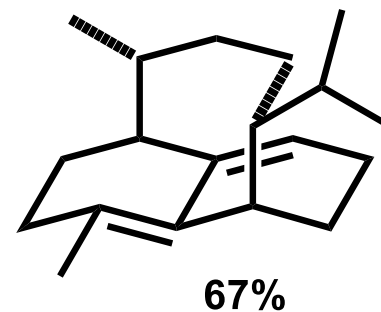
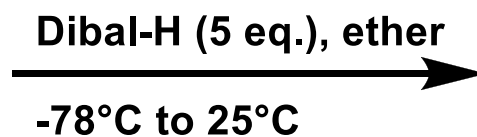
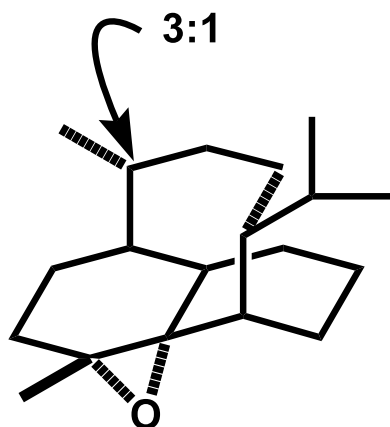
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Epoxide Opening



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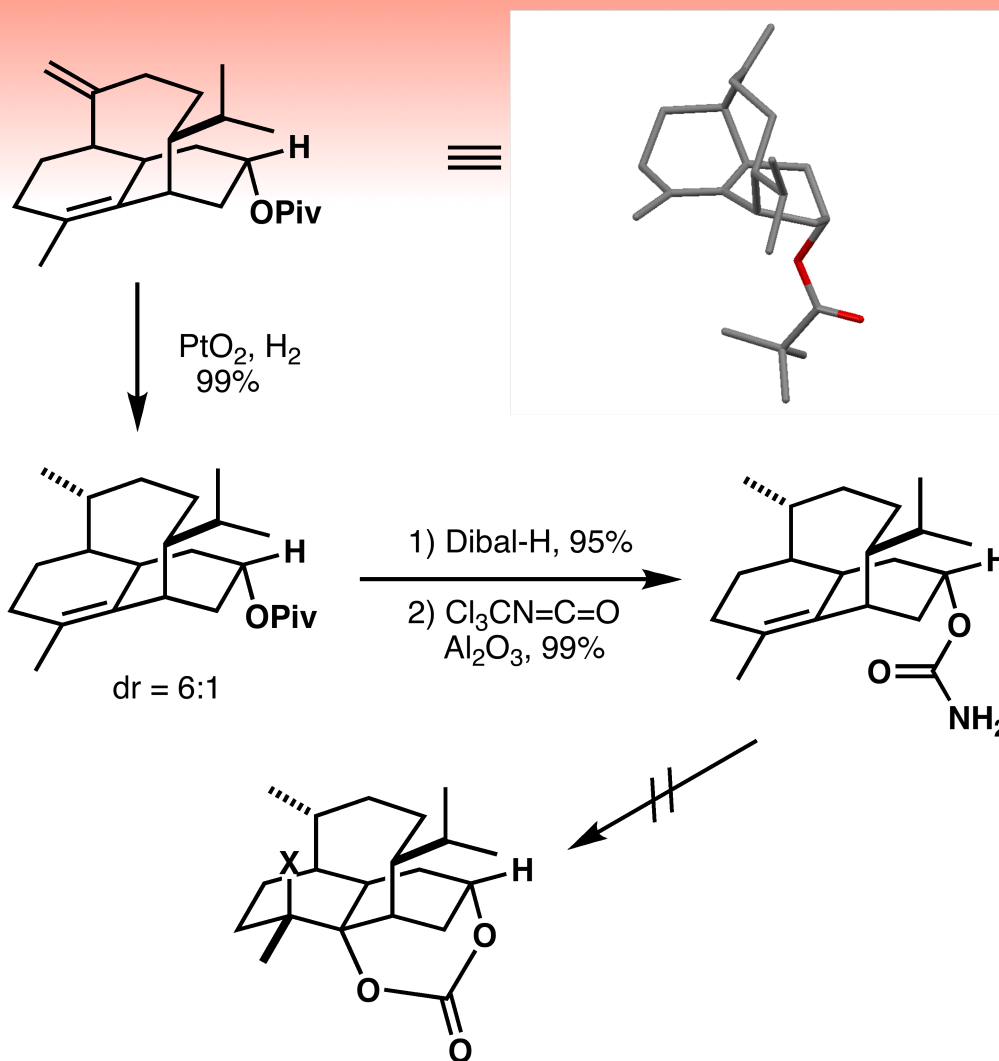
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Ultime effort



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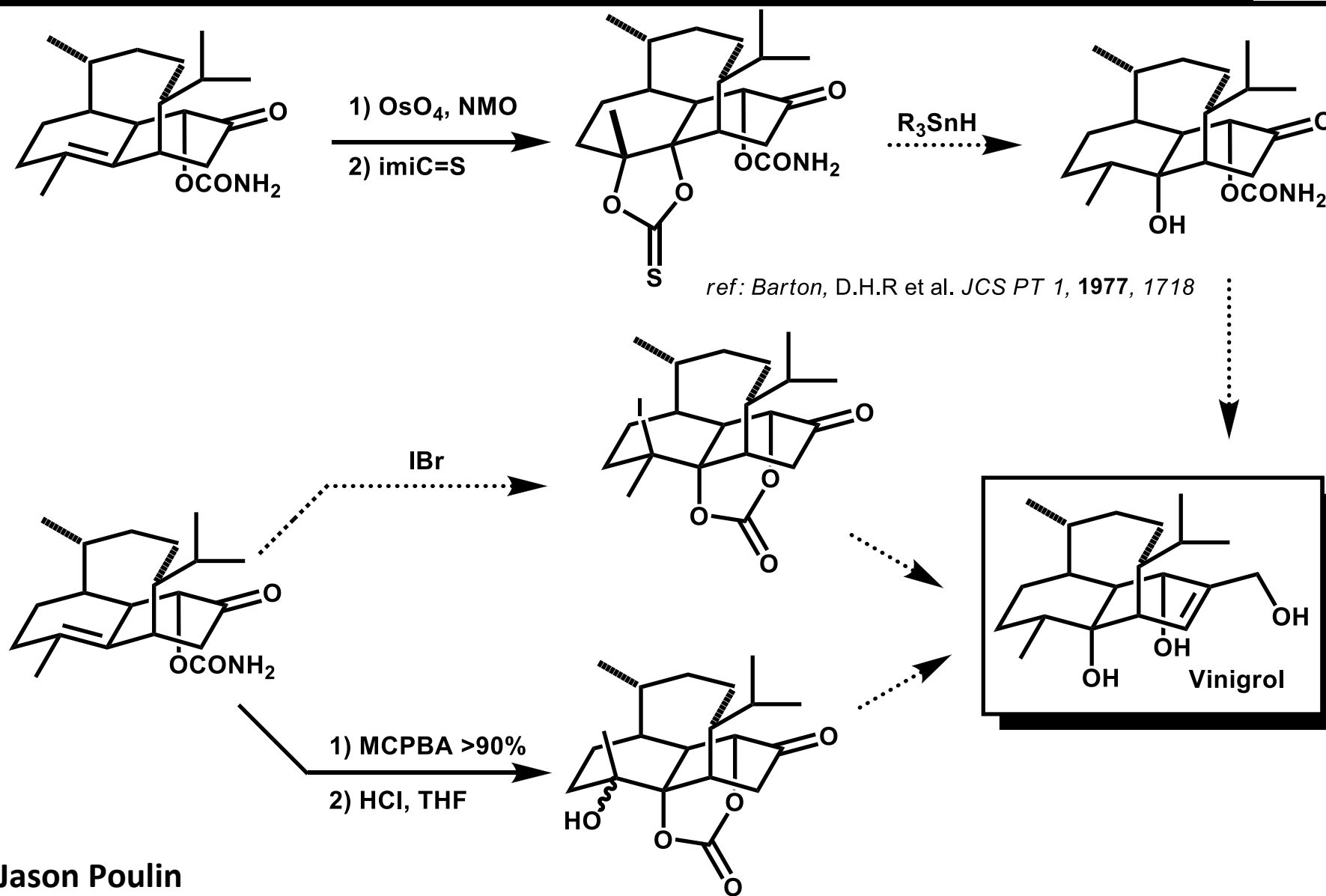
Christiane Grisé

Proposed end game



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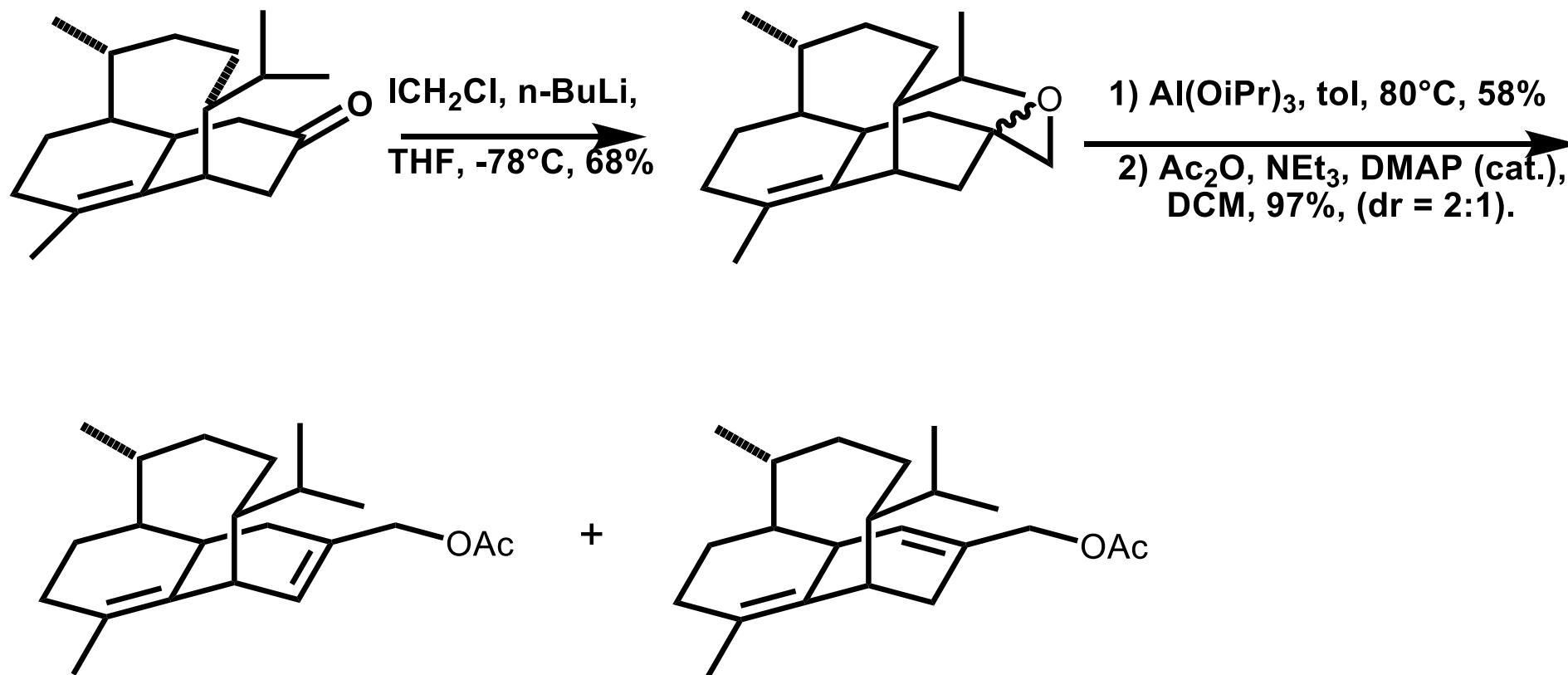


Second Generation



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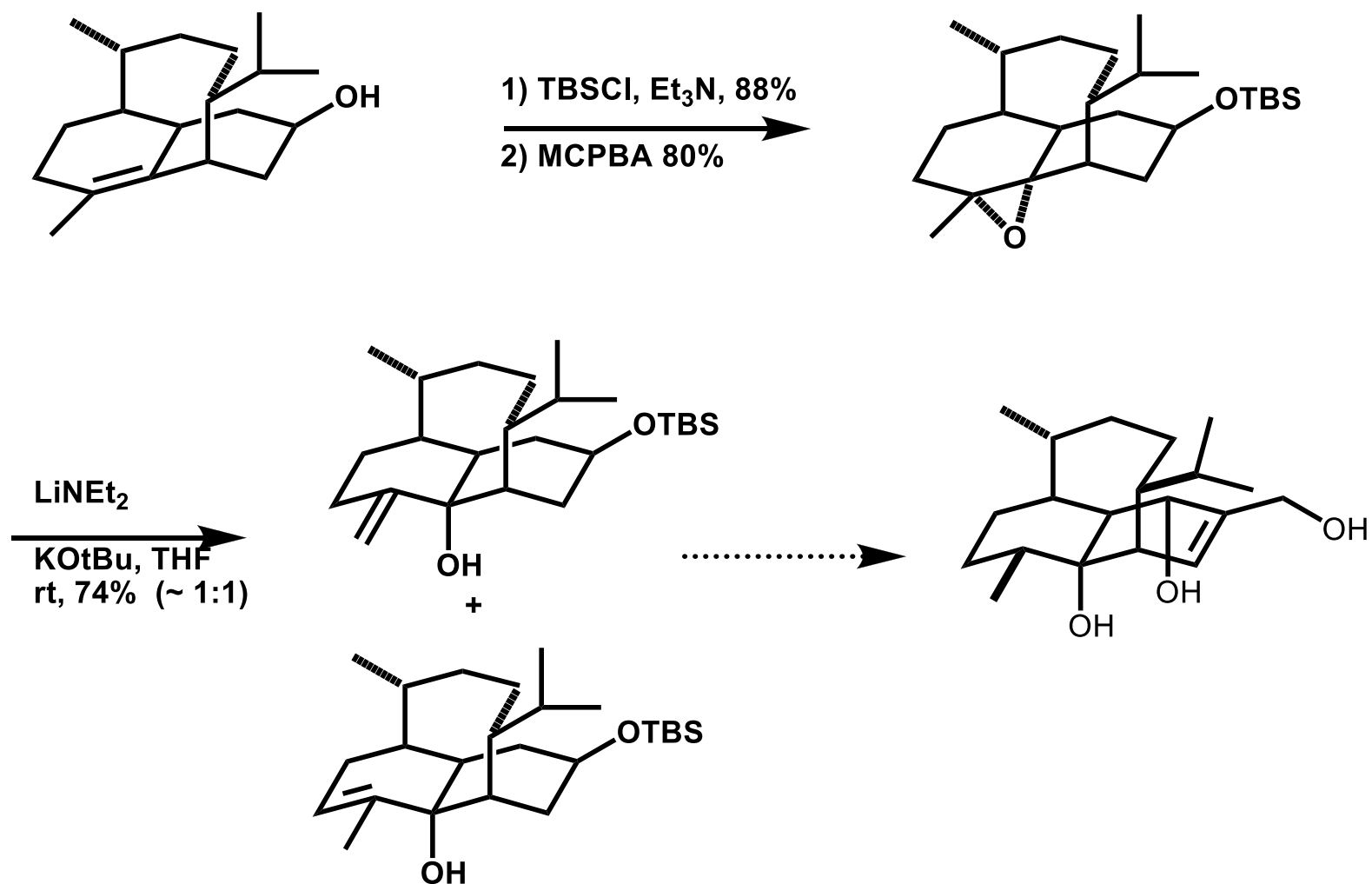
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Second Generation



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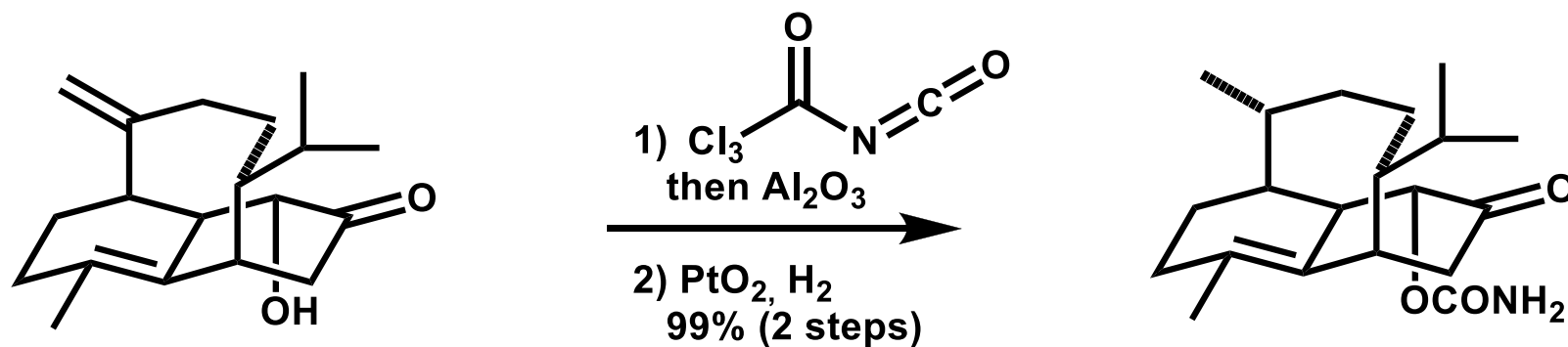
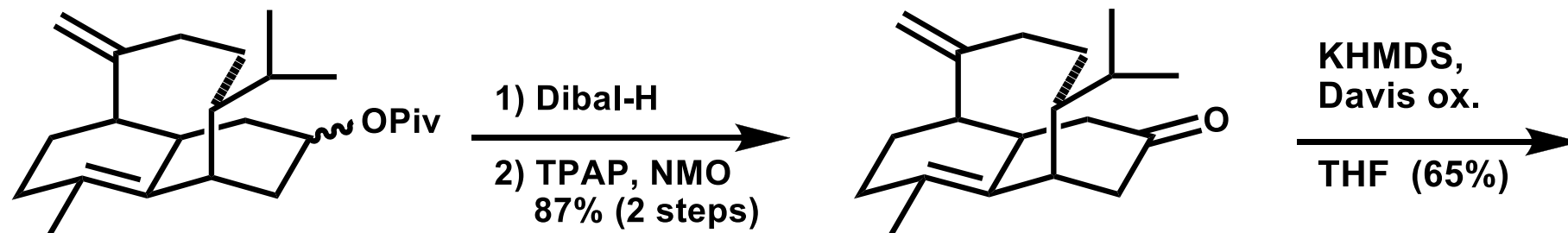
Christiane Grisé, Jason Poulin.

Proposed End Game



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Only one regioisomer ! (> 10:1)

Only one stereoisomer ! (>10:1)

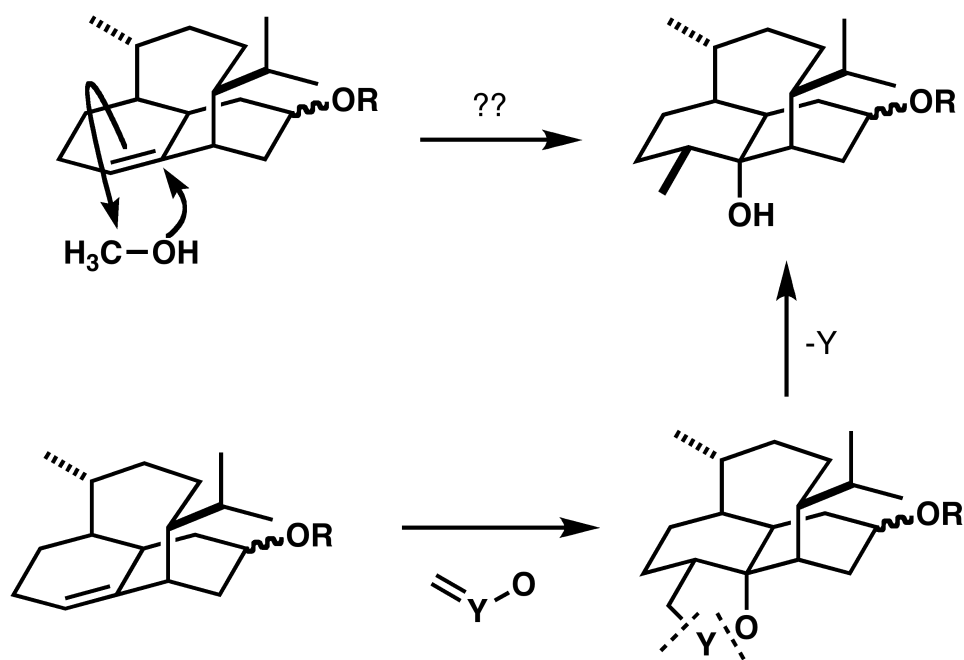
Jason Poulin

Installation of the methyl



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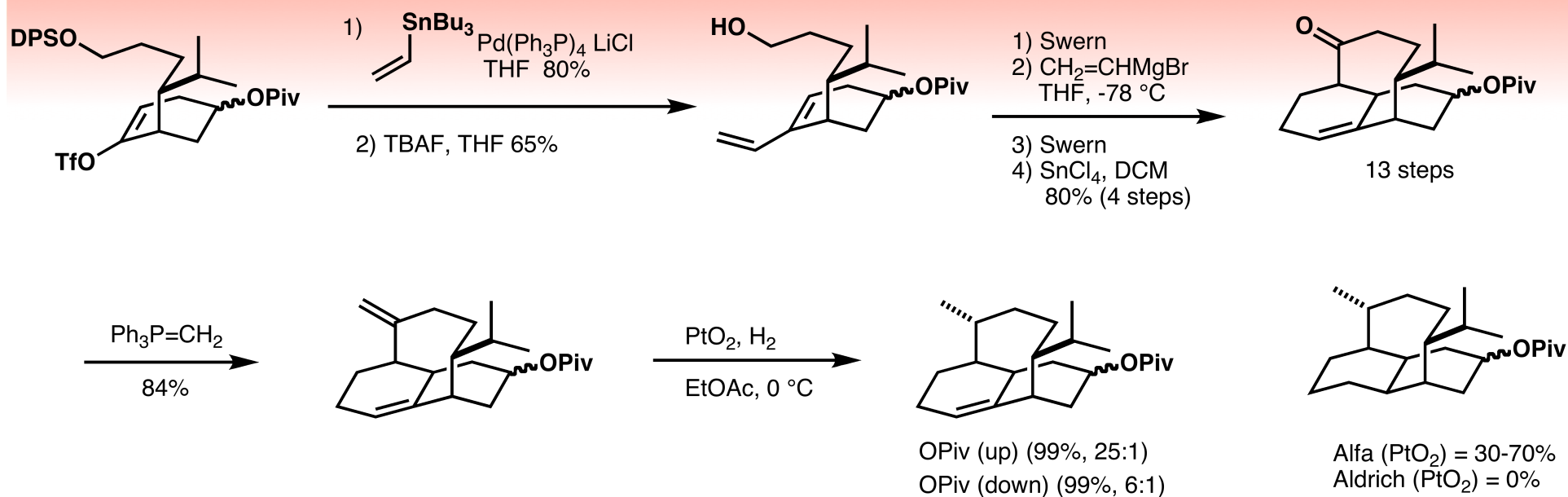


Final Stretch



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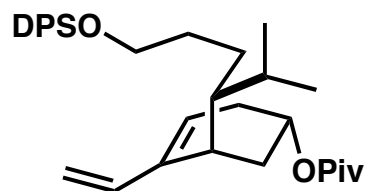
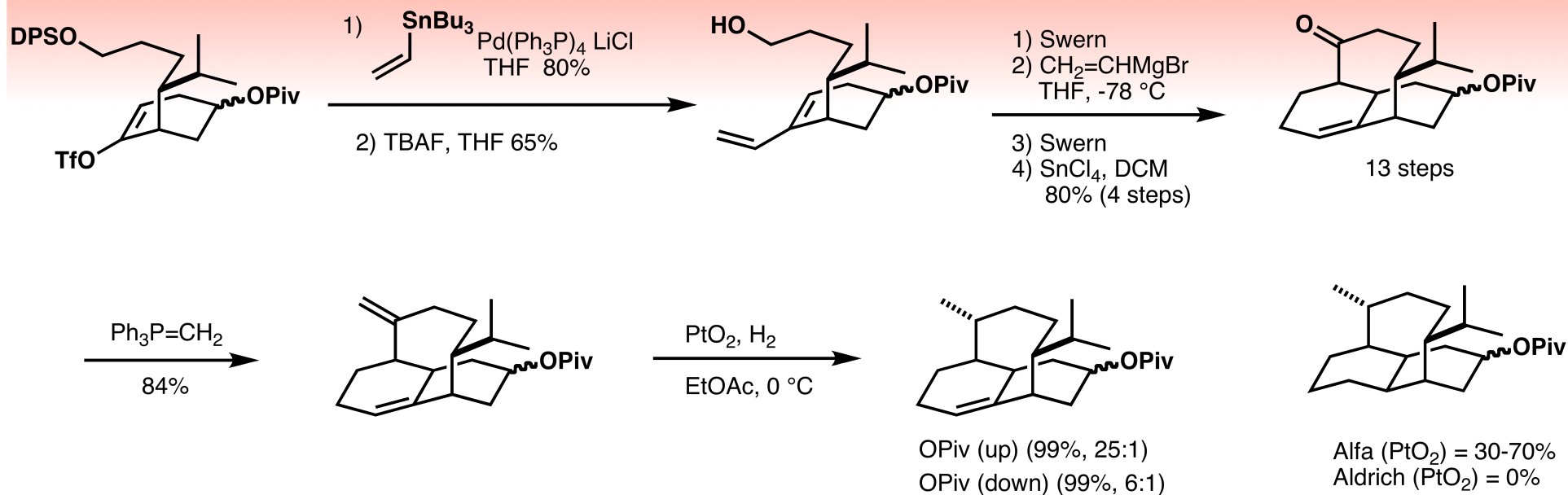


Final Stretch

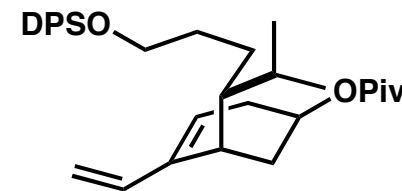


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- 1) Dibal-H, DCM, -78°C , 94%
- 2) ArCO_2H , DIAD, Ph_3P , THF
- 3) NaOH , MeOH/THF, 70% (2 steps)
- 4) PivCl , Et_3N , DMAP, DCM, 95%



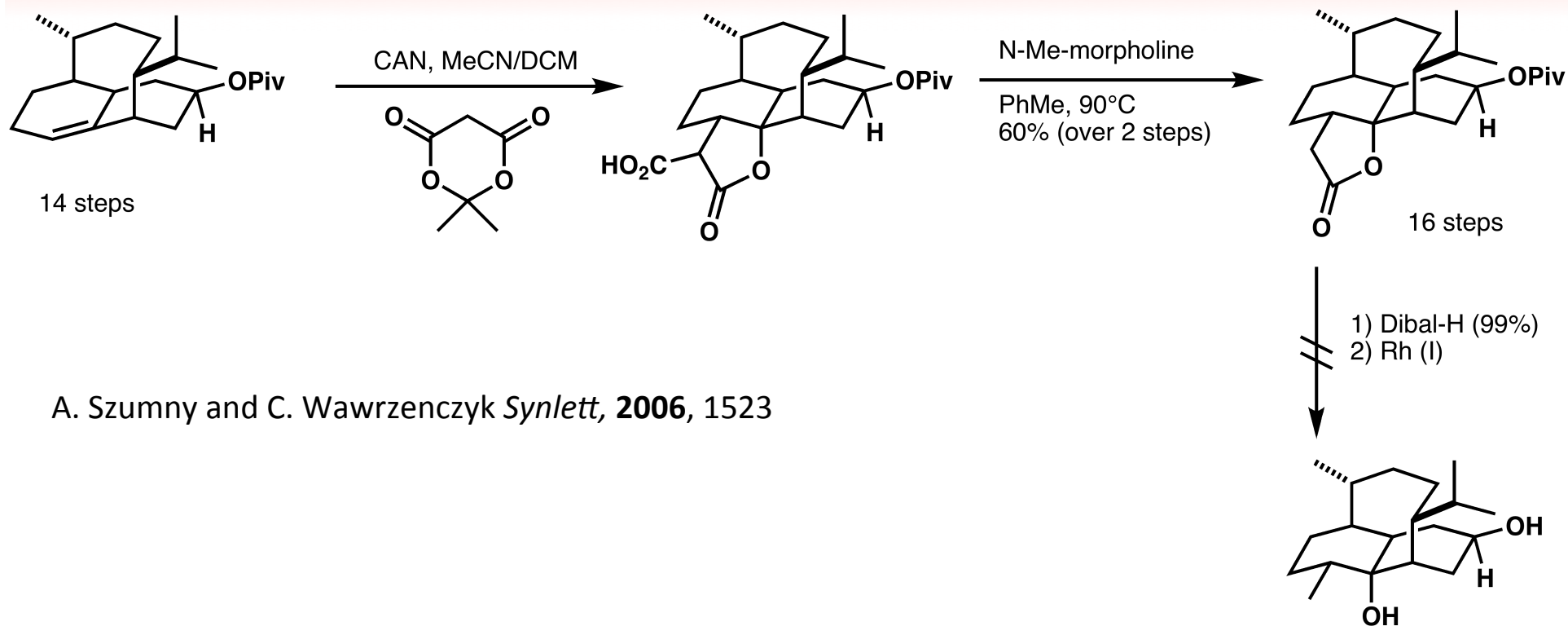
Jason Poulin

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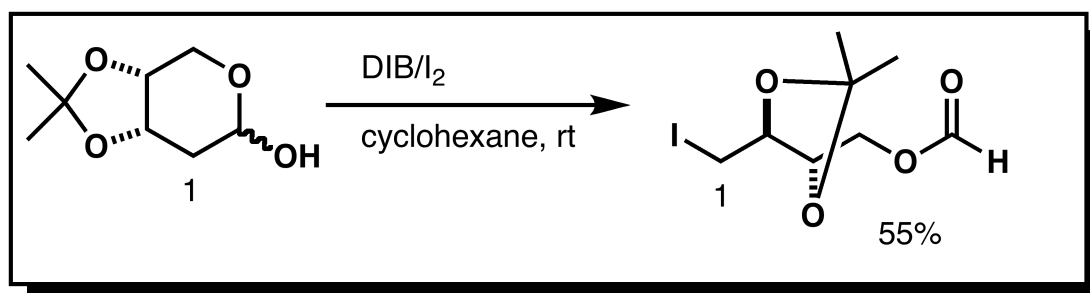
A. Szumny and C. Wawrzenczyk *Synlett*, **2006**, 1523

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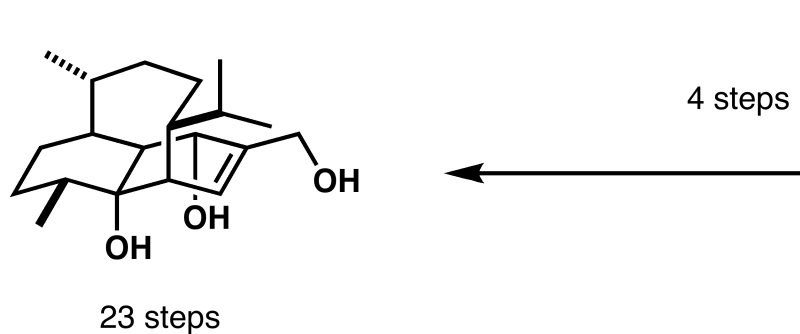
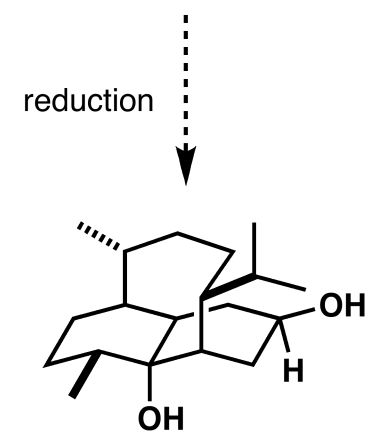
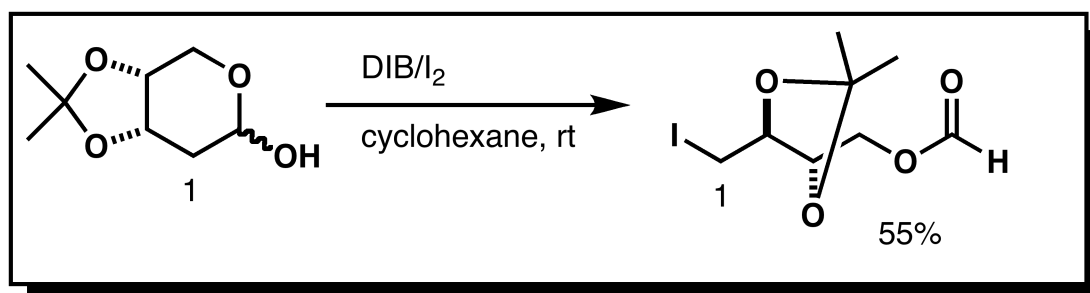
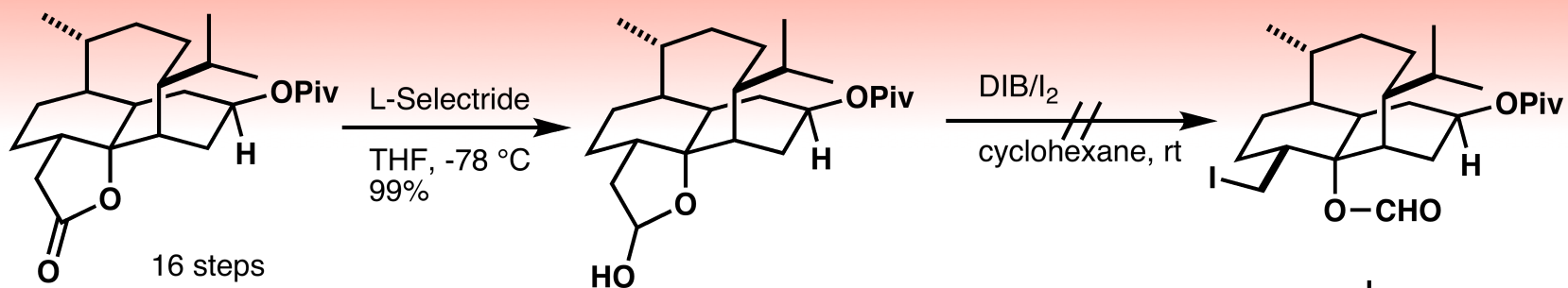
Suarez, E.; *et al.* *Angew. Chem Int., Ed*, **1992**, 31,772

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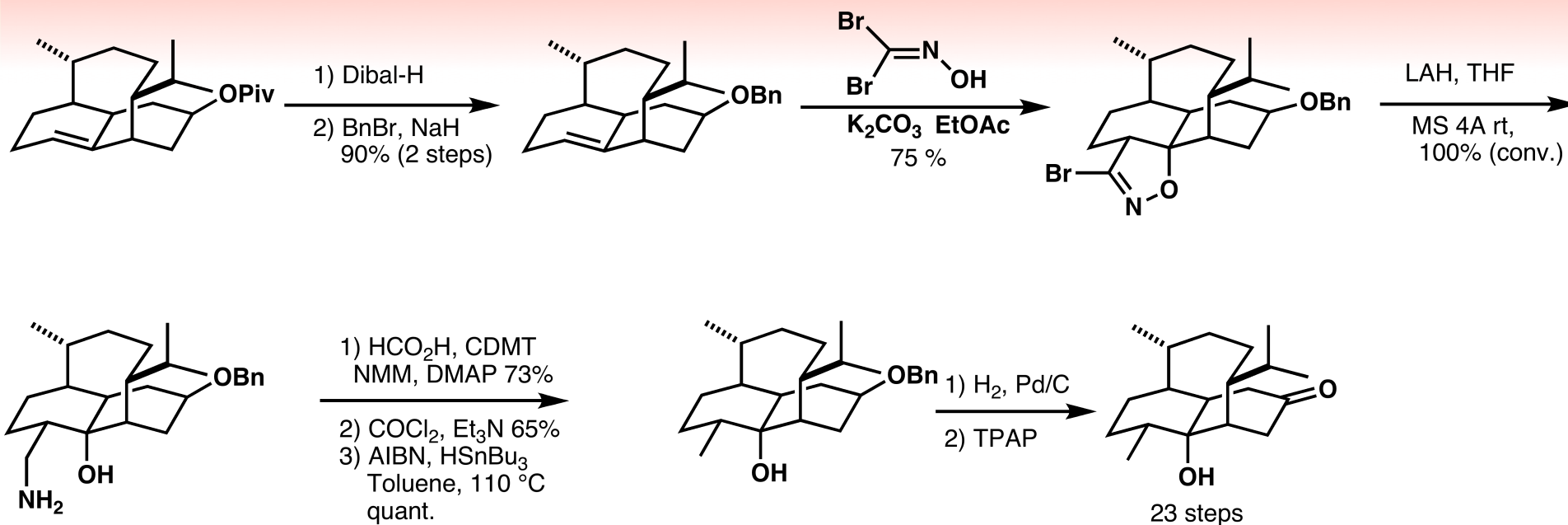


End Game



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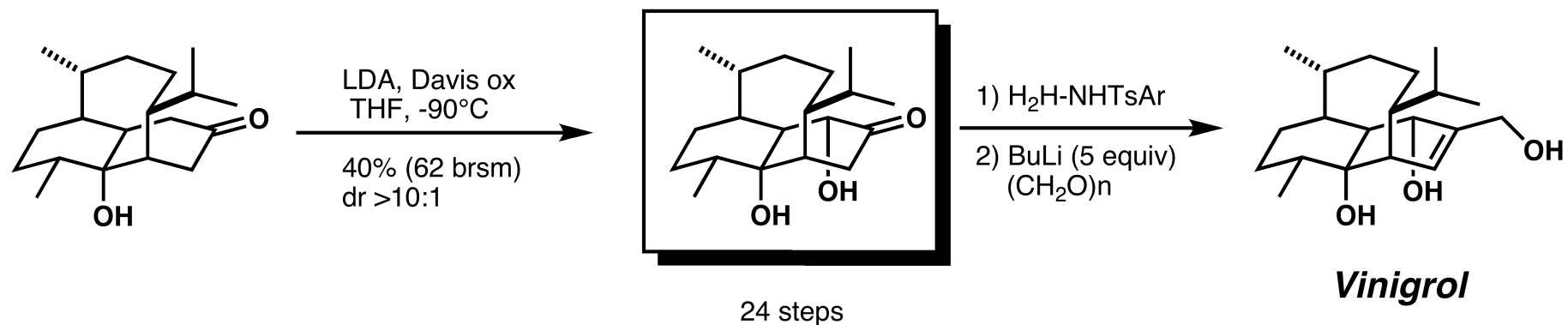
1) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *Tetrahedron Lett.* **1984**, 25, 48. 2) Maimone, T. J., Shi, J.; Ashida, S, Baran, P. J. *Am. Chem. Soc.* **2009**, 131, 17066.

End Game



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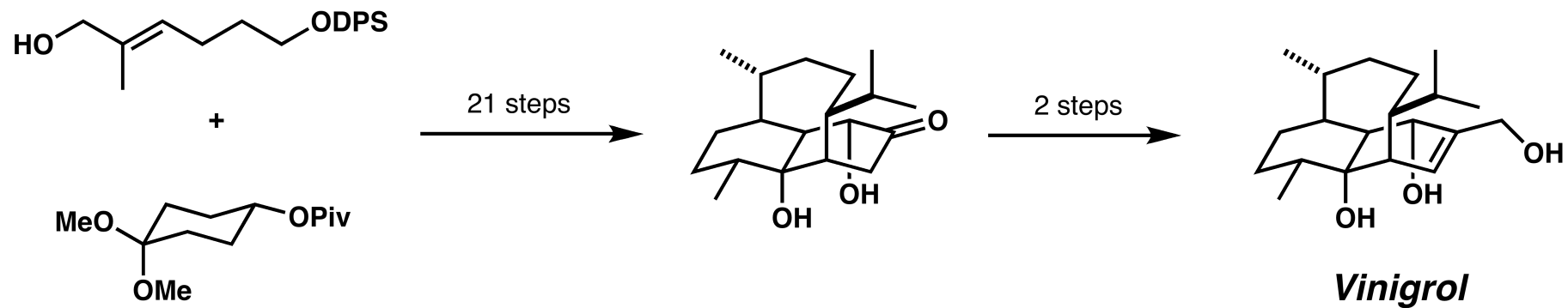
Poulin, J.; Gris -Bard, C. M.; Barriault, L. *Angew. Chem. Int. Ed.* **2012**, 51, 2111.

Conclusion



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Poulin, J.; Gris -Bard, C. M.; Barriault, L. *Angew. Chem. Int. Ed.* **2012**, 51, 2111.