

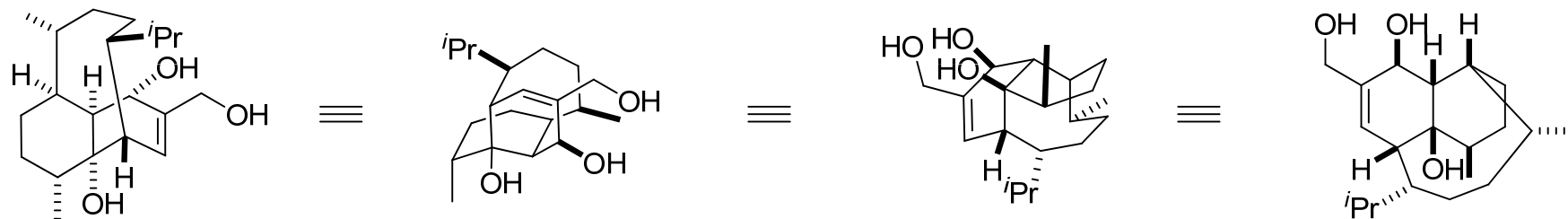
Vinigrol

Anne-Marie Dechert

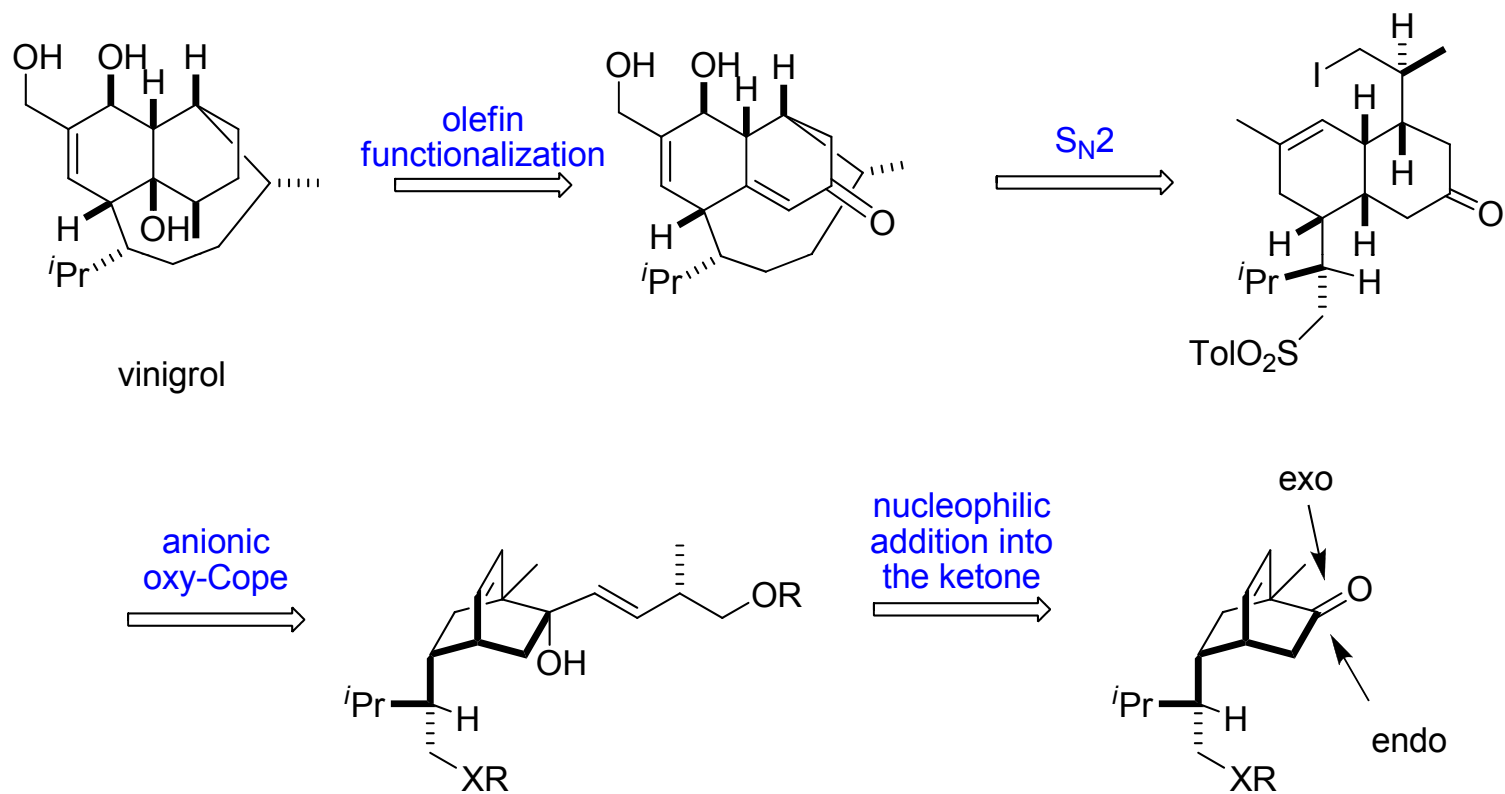
April 23, 2010

Structural Features and Biological Activity

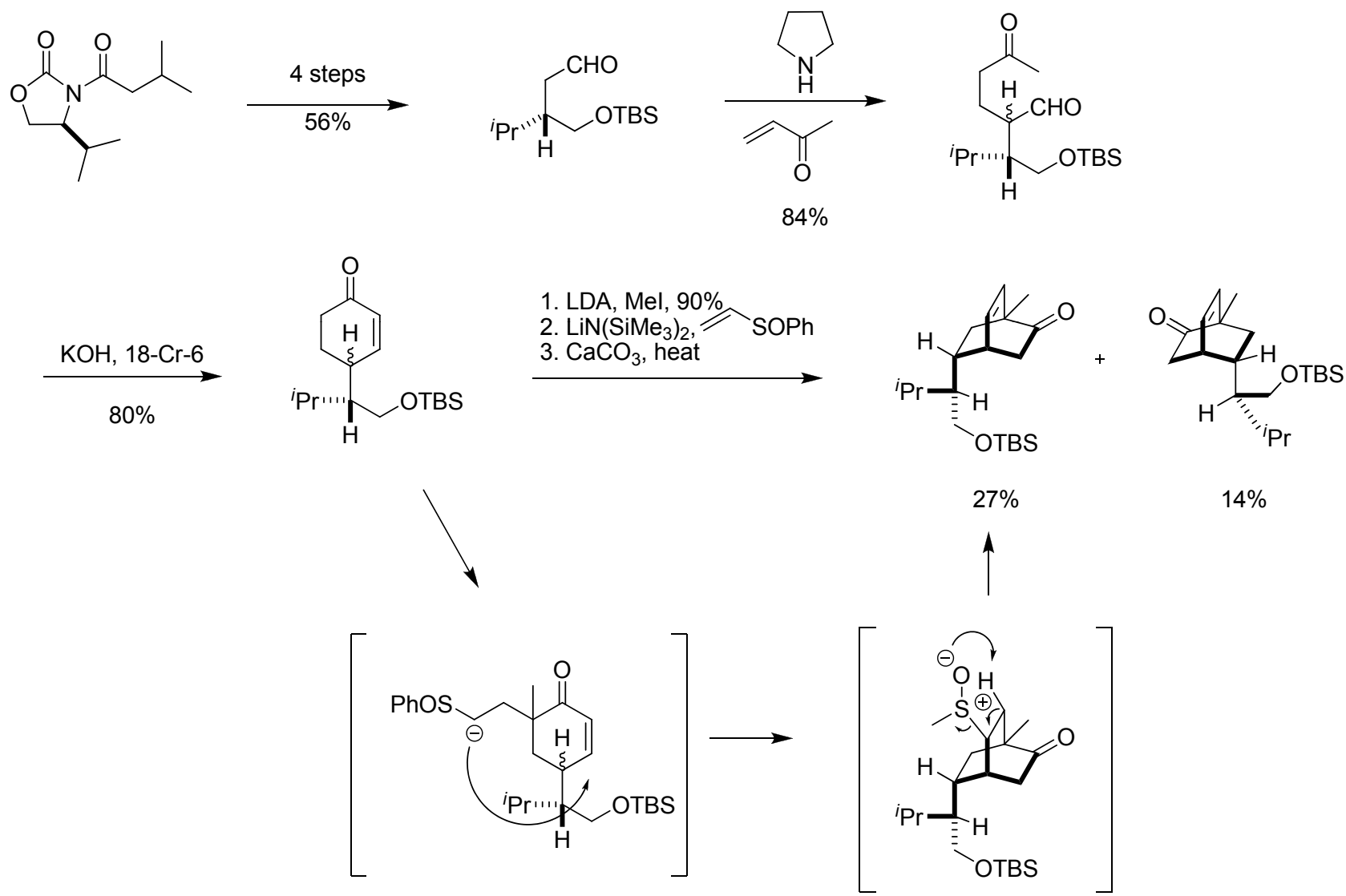
- Isolated in 1987 from the fungal strain *Virgaria nigra* F-5408 by Ando and coworkers
- Structure elucidated by X-Ray and spectroscopic studies
- Biological: Anti-hypertensive, platelet aggregation inhibiting properties, also capable of arresting the progression of HIV to AIDS, nerve stem cell proliferation promoter
- Structural complexity: contains a *cis*-decalin bridged by an 8 membered ring containing 8 contiguous stereocenters
- Partial Syntheses: Barriault, Hanna, Fallis, Njardarson, Corey, Matsuda, Paquette
- Total Synthesis: Baran (2009)
- Not covered in today's talk: Barriault, Corey, Mehta, Matsuda



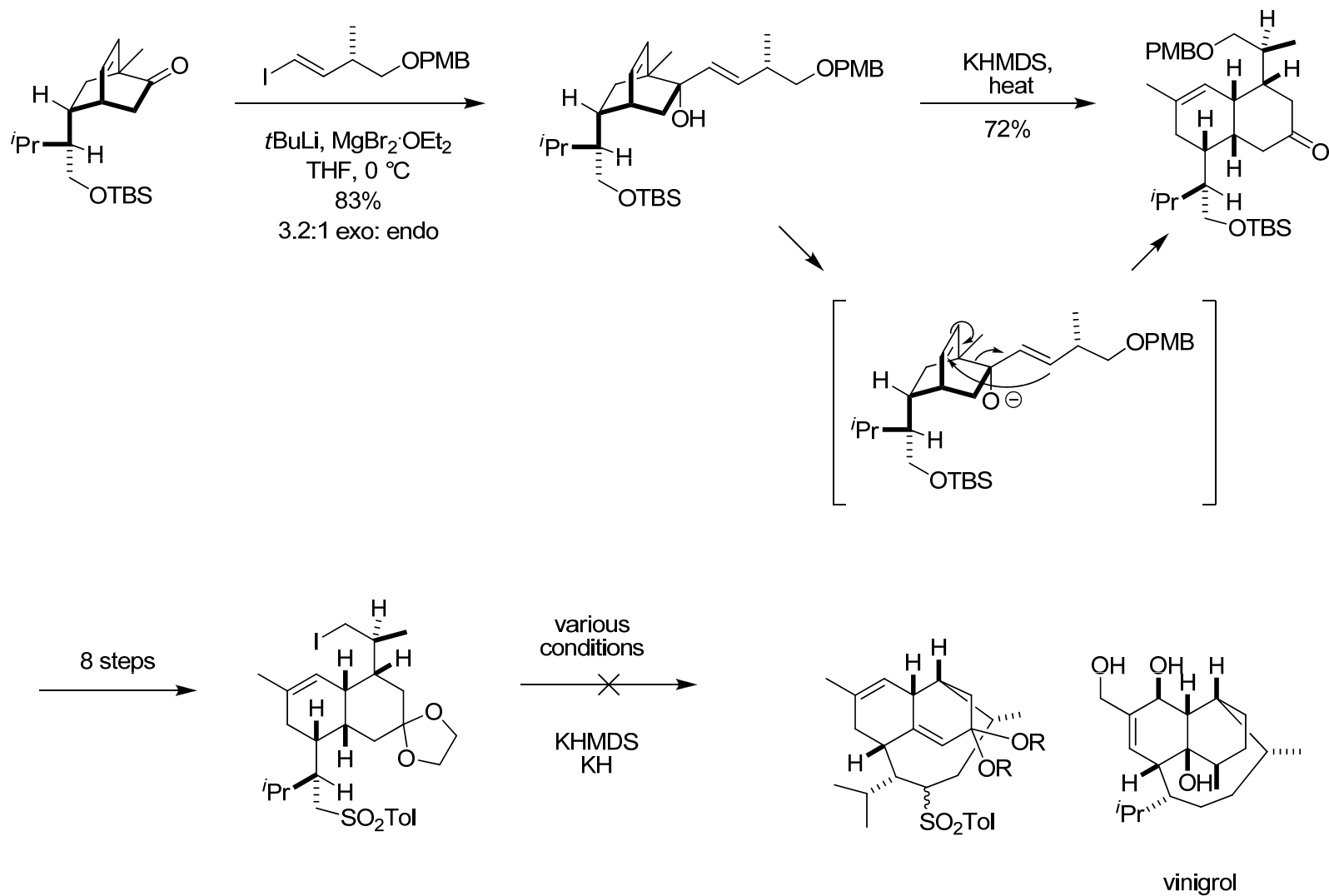
Paquette's Retrosynthesis



Synthesis of the Oxy Cope Precursor



Attempted End Game Strategy



Model Calculations

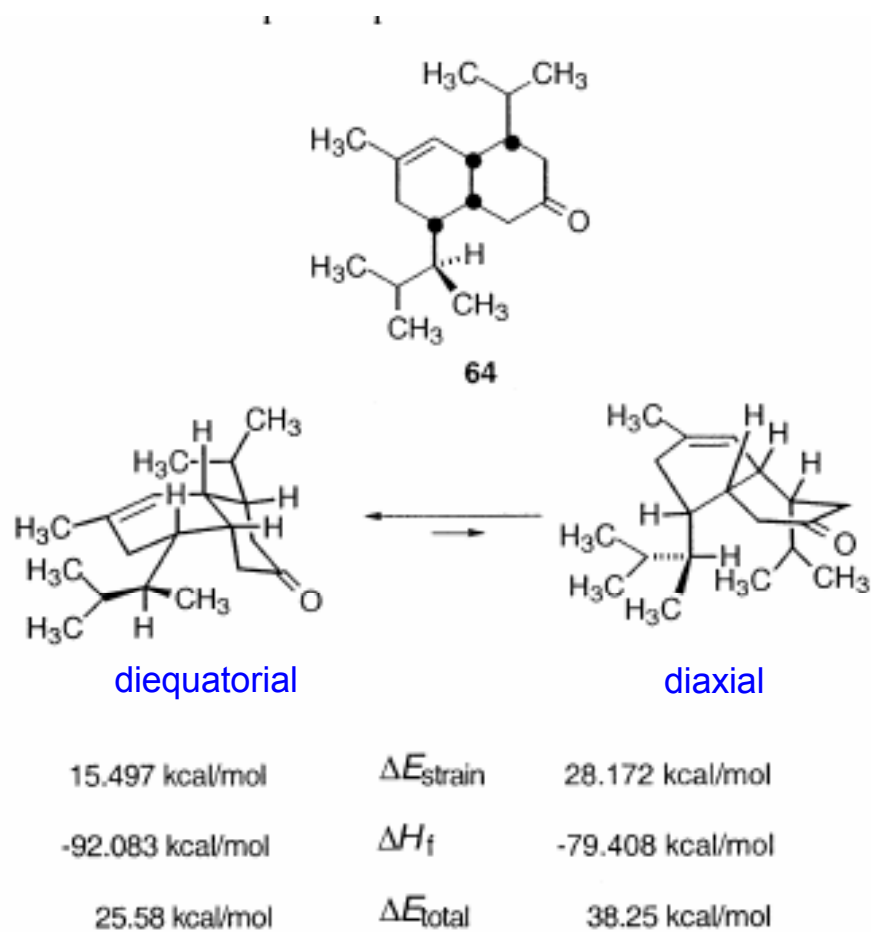
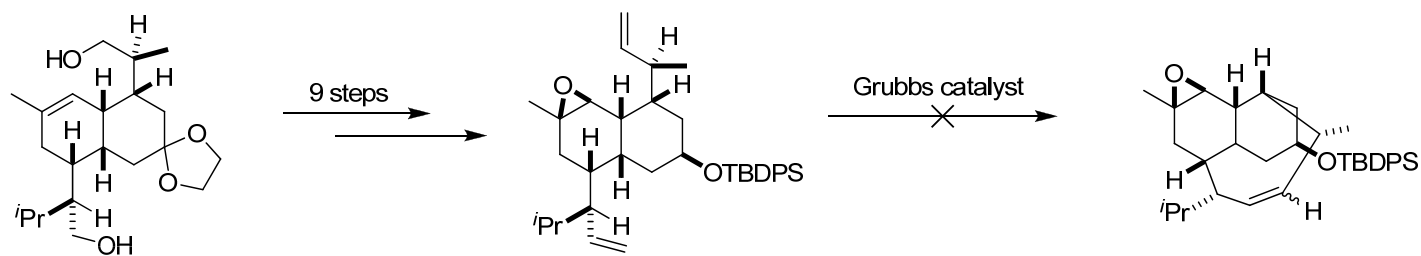
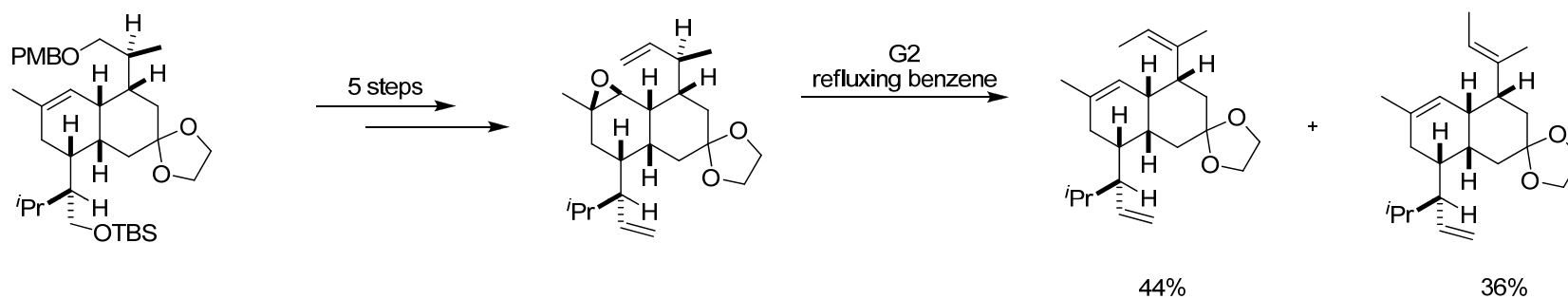
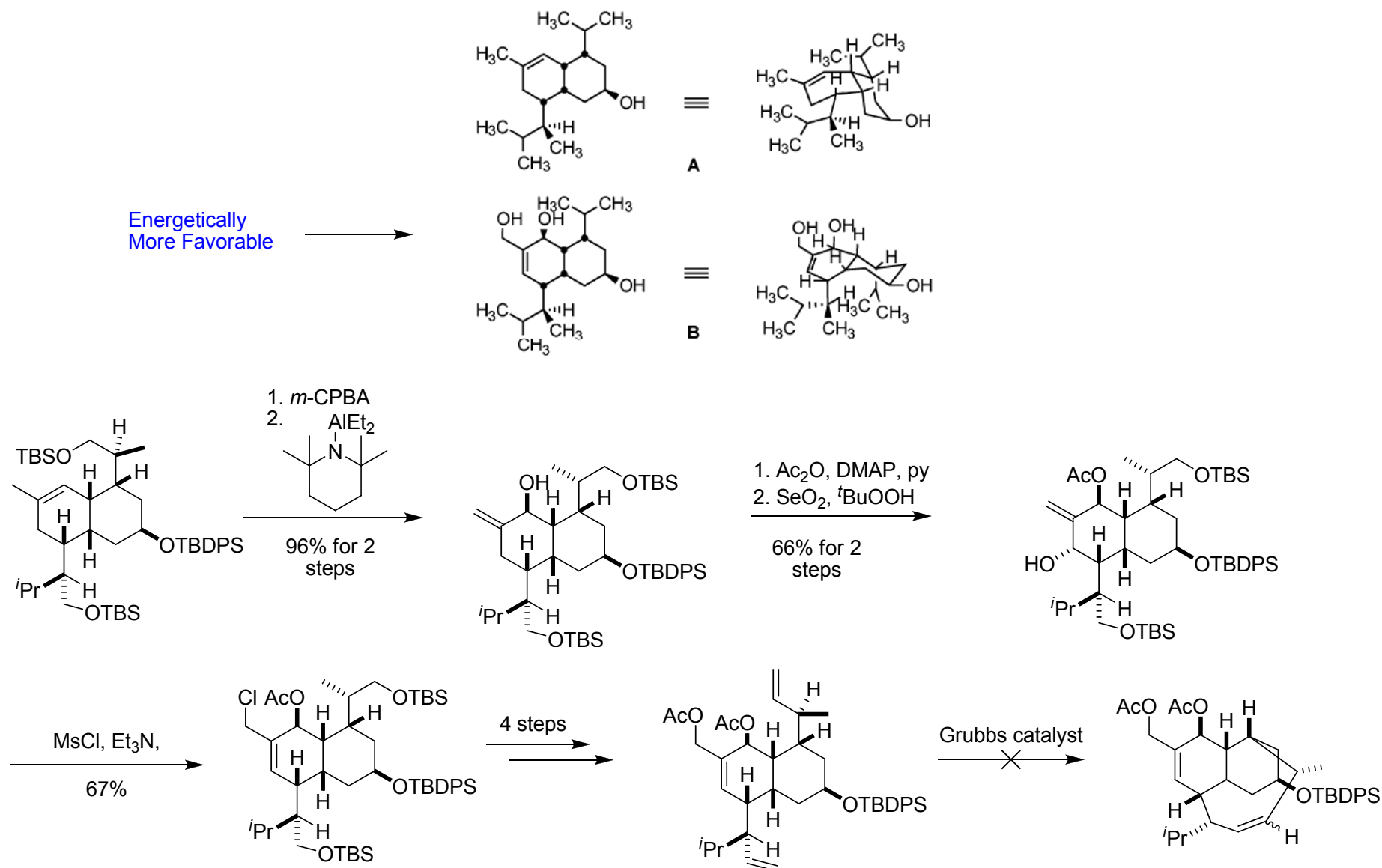


FIGURE 2. Energy separating the diequatorial and diaxial conformers of **64**.

A Ring Closing Metathesis Strategy



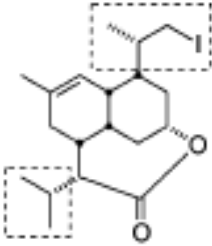
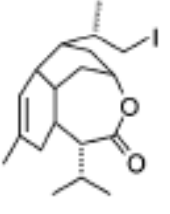
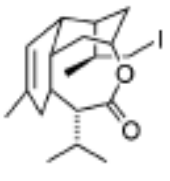
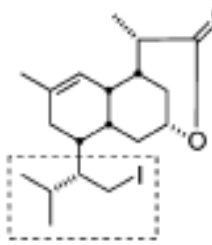
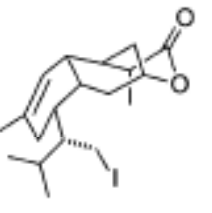
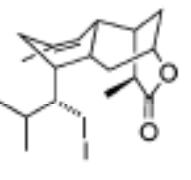
Migration of the Endocyclic Olefin



Paquette, L. A.; Efremov, I.; Liu, Z. *J. Org. Chem.* **2005**, *70*, 505.

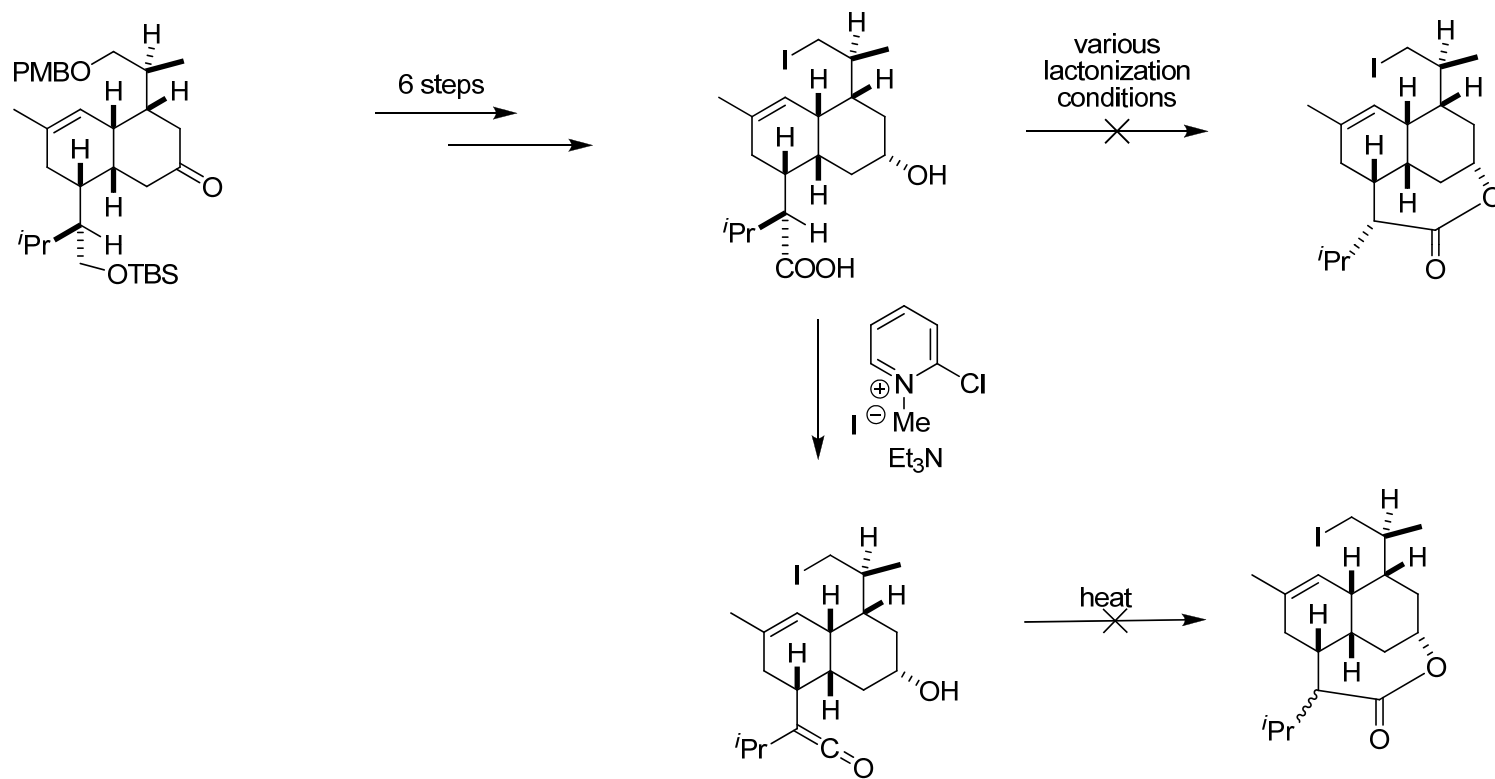
Use of a Lactone Bridge as a Conformational Lock

TABLE 1. Calculated Steric Energies for 3 and 5

Iodolactone ^a	More stable equatorial conformer	Less stable axial conformer	ΔE_{steric} , kcal/mol
 3	 3a	 3b	0.2
 5	 5a	 5b	4.7

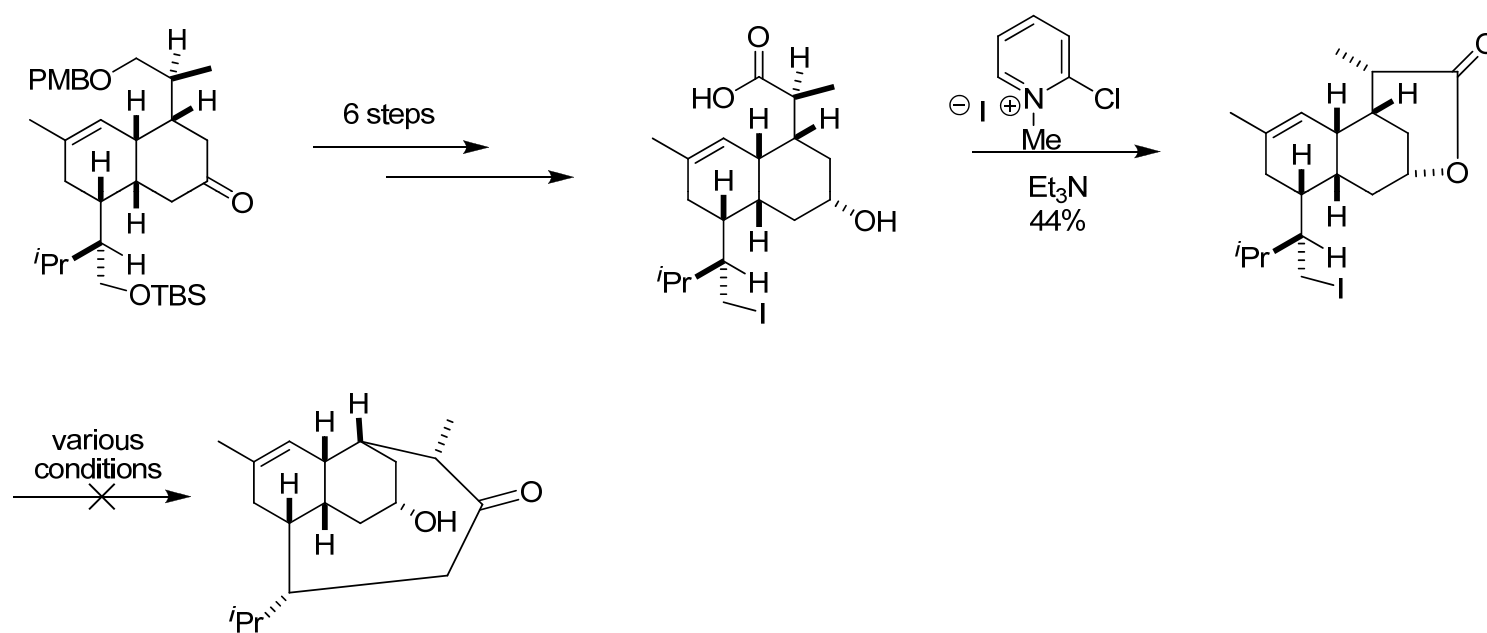
^a For the calculations, the encased substituents were replaced by methyl groups.

Attempts to Synthesize the Lactone



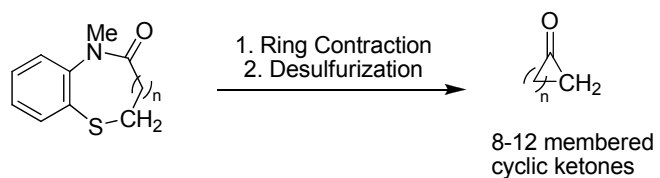
Paquette, L. A.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 510.

Cyclization to Form the 8-Membered Ring?

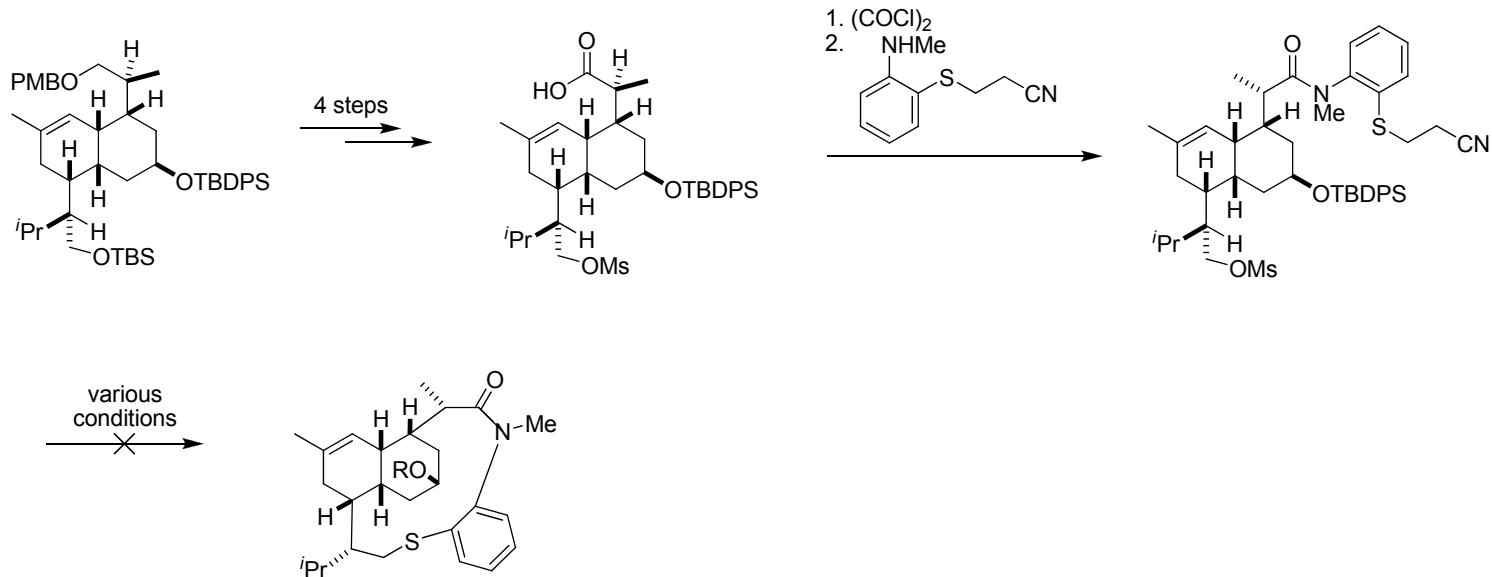
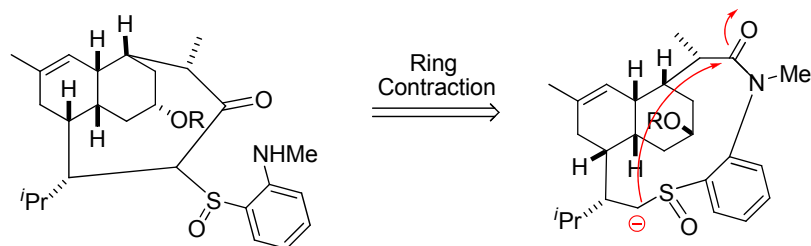


A Ring Contraction Strategy

Literature Precedent:

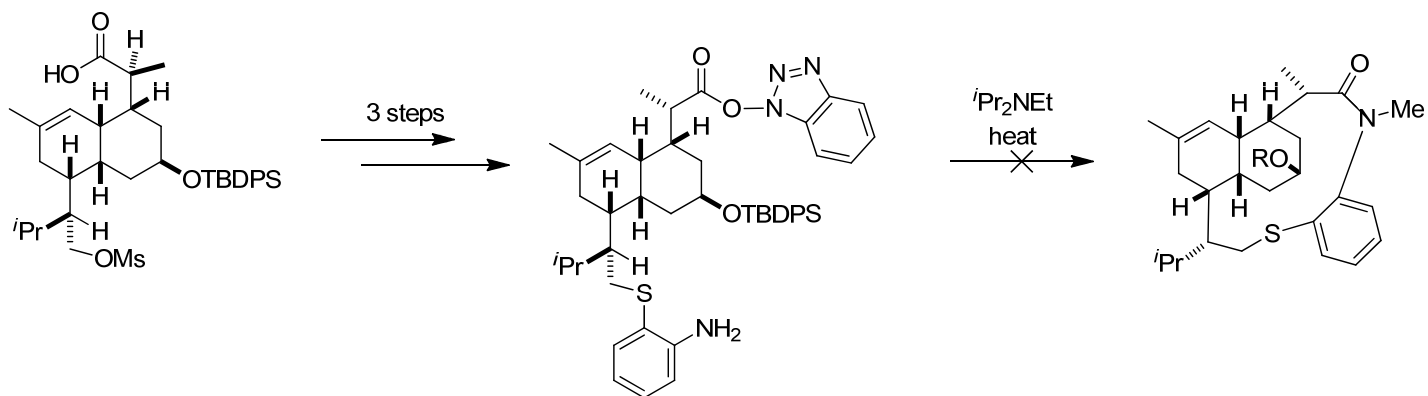
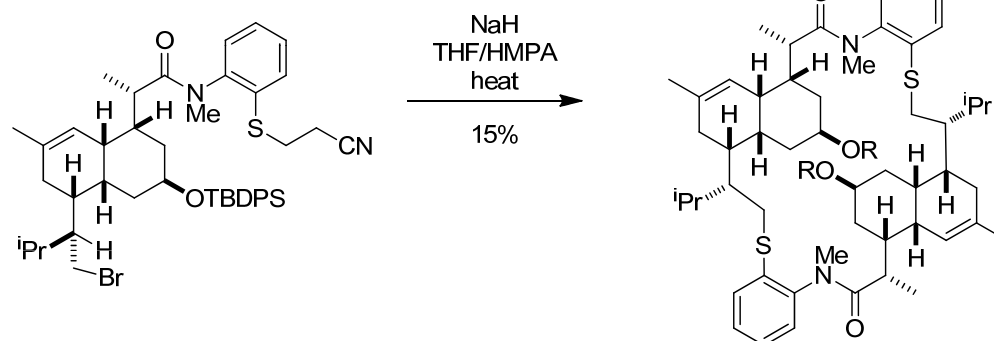
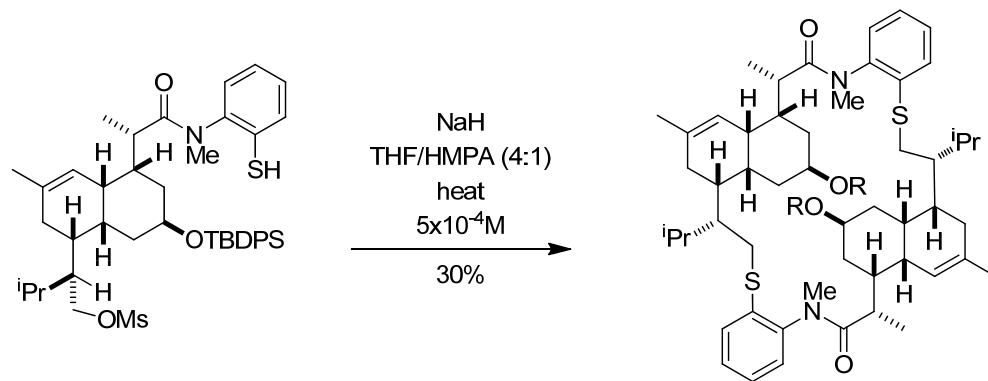


Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1983**, 31, 454.



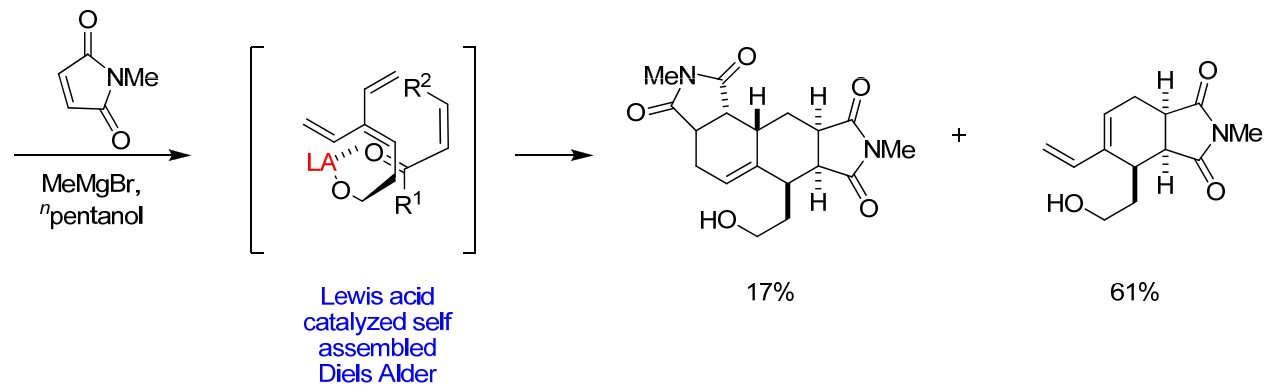
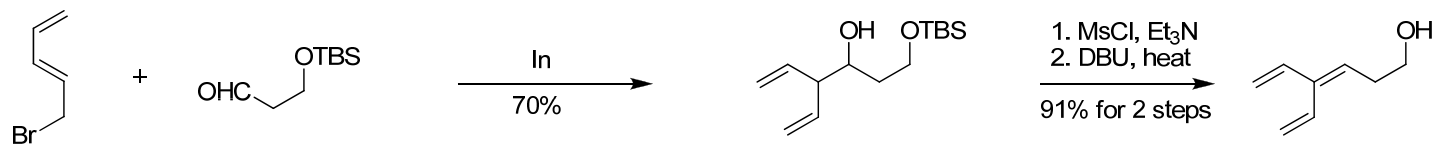
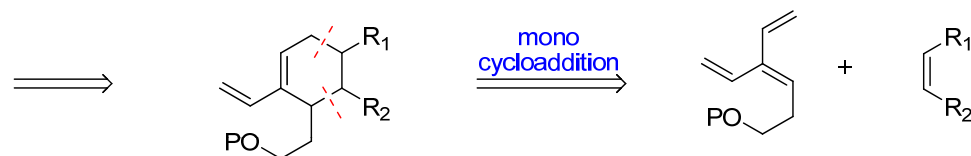
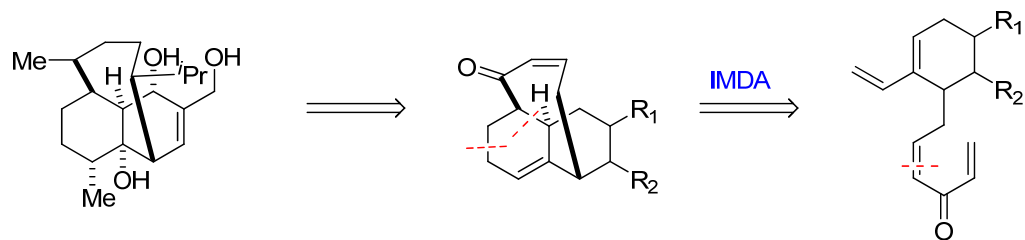
Paquette, L. A.; Liu, Z.; Efremov, I. *J. Org. Chem.* **2005**, 70, 514.

A Final Attempt



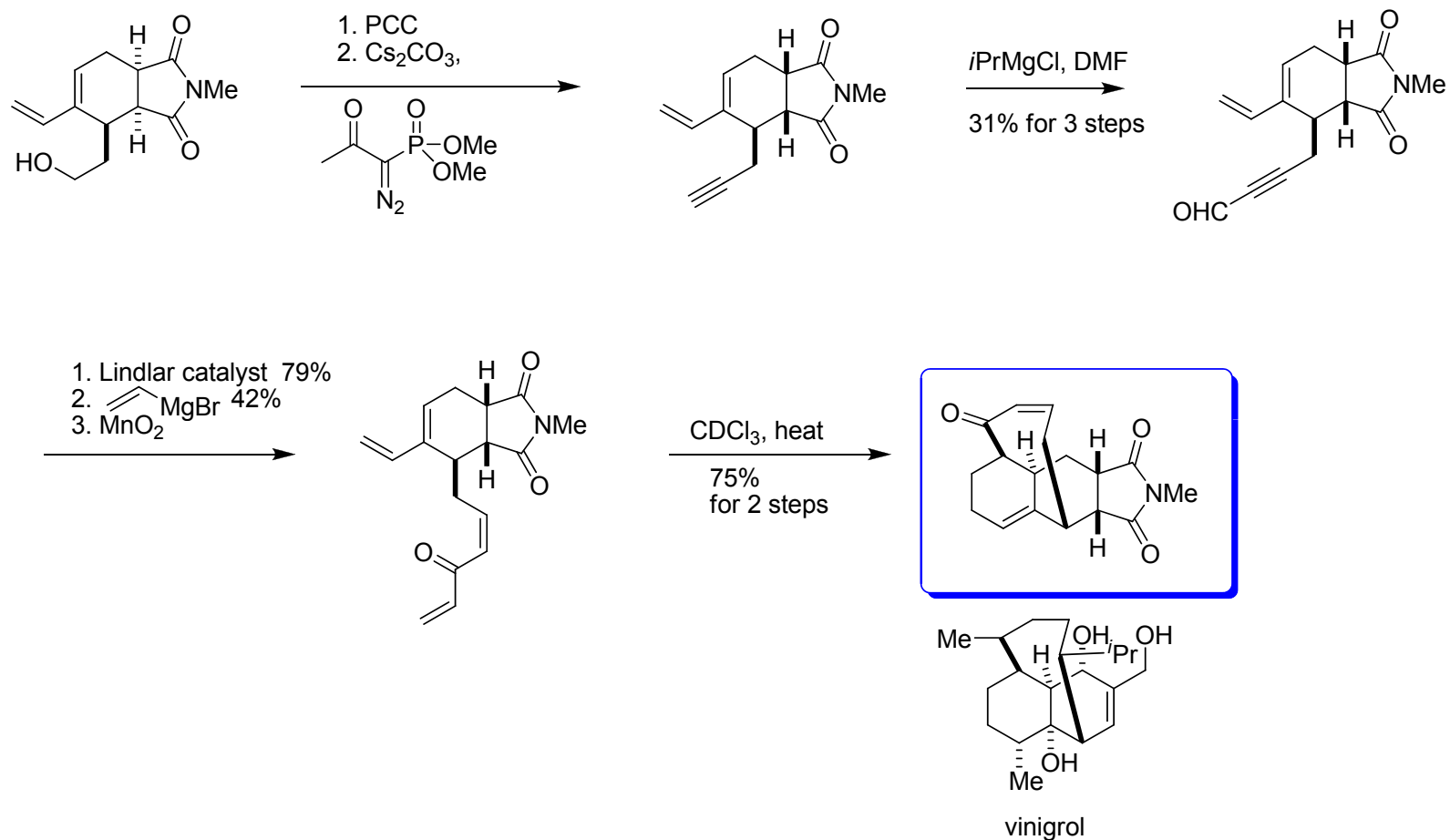
Paquette, L. A.; Liu, Z.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 514.

Fallis' Retrosynthesis

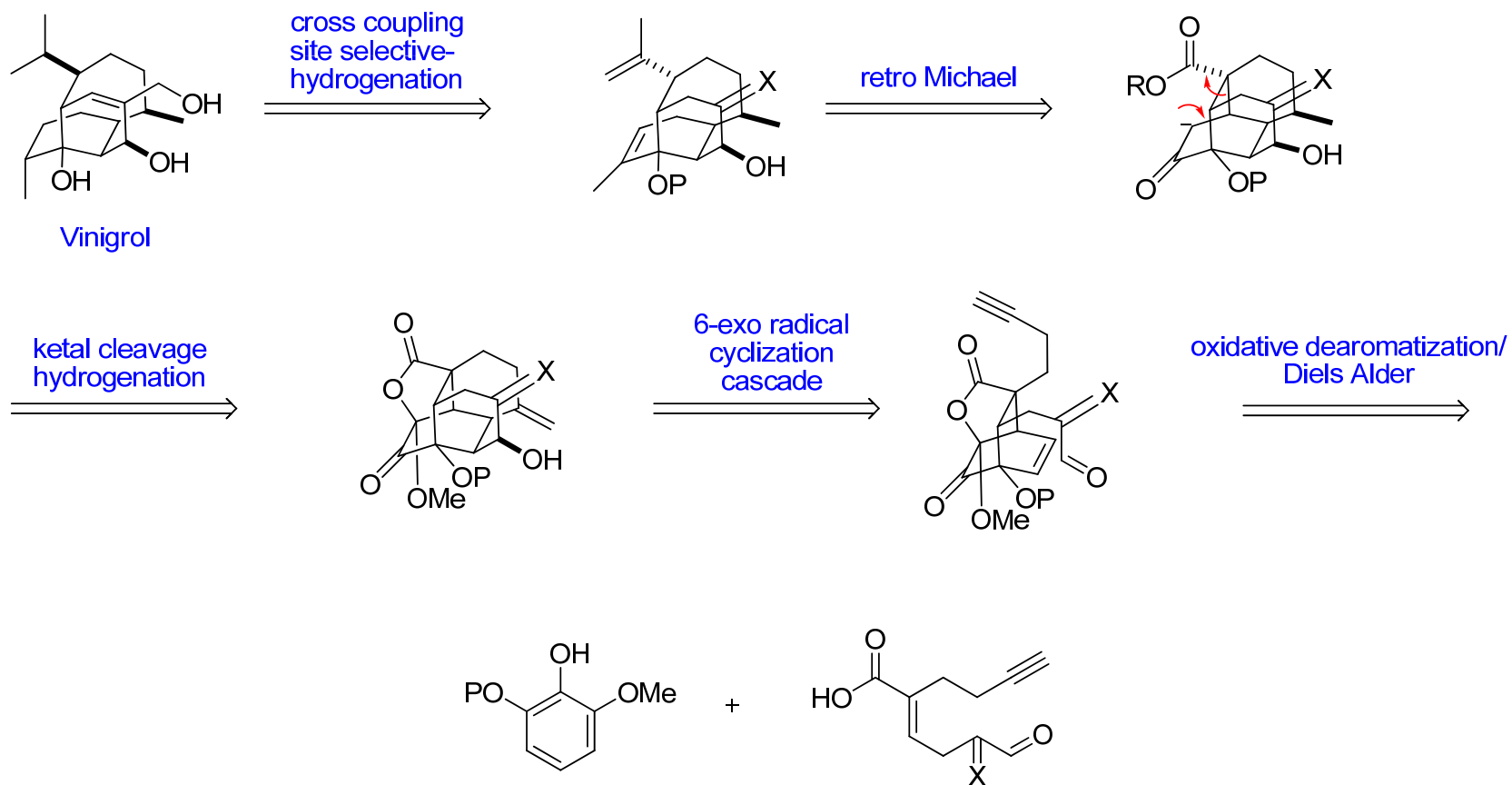


Souweha, M.; Arab, A.; AsSimon, M.; Fallis, A. G. **2007**, *9*, 615.
 Souweha, M.S.; Enright, G. D.; Fallis, A. G. *Org. Lett.* **2007**, *9*, 5163.

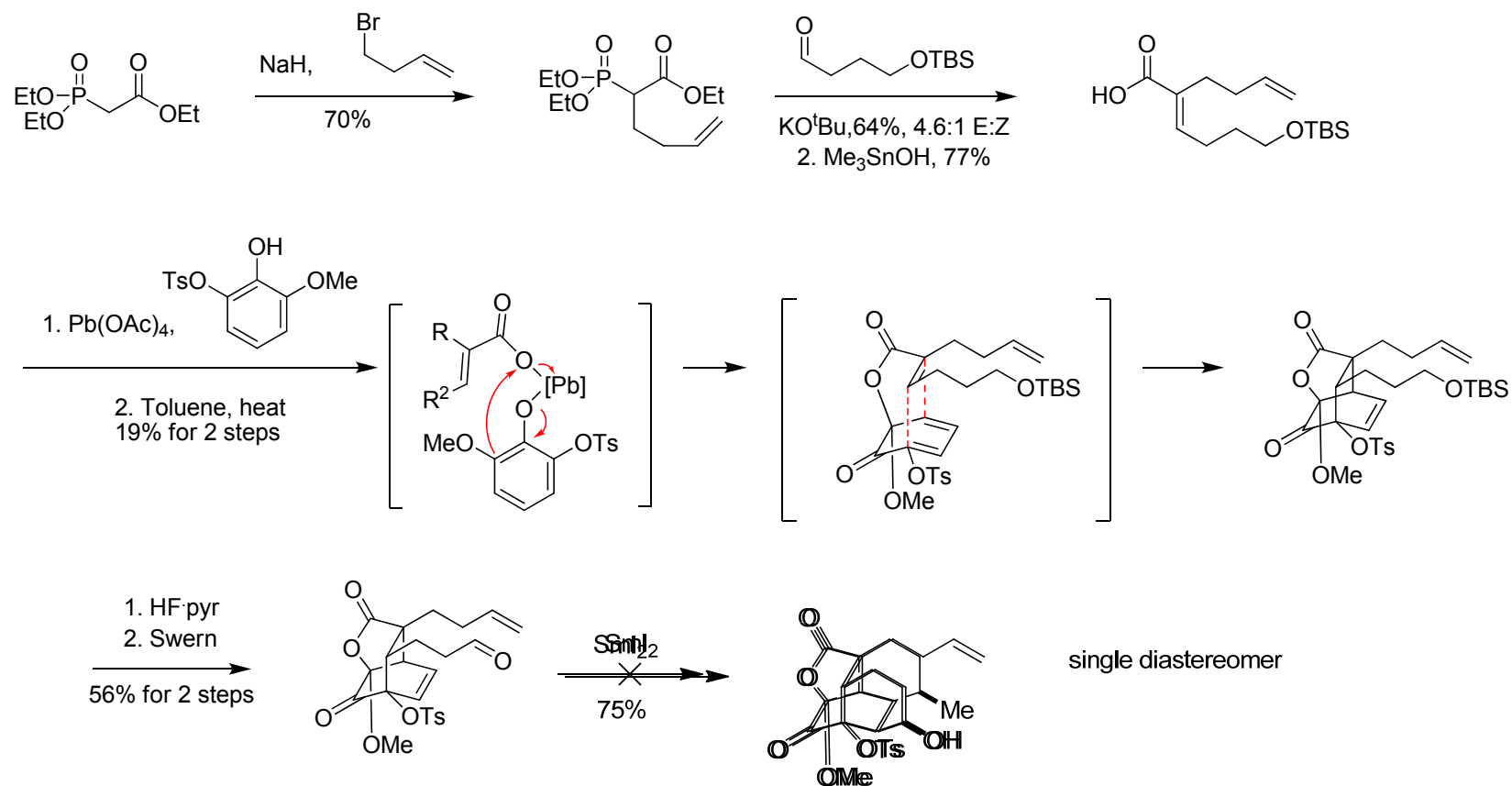
Fallis' Synthesis of the Tricyclic Core of Vinigrol



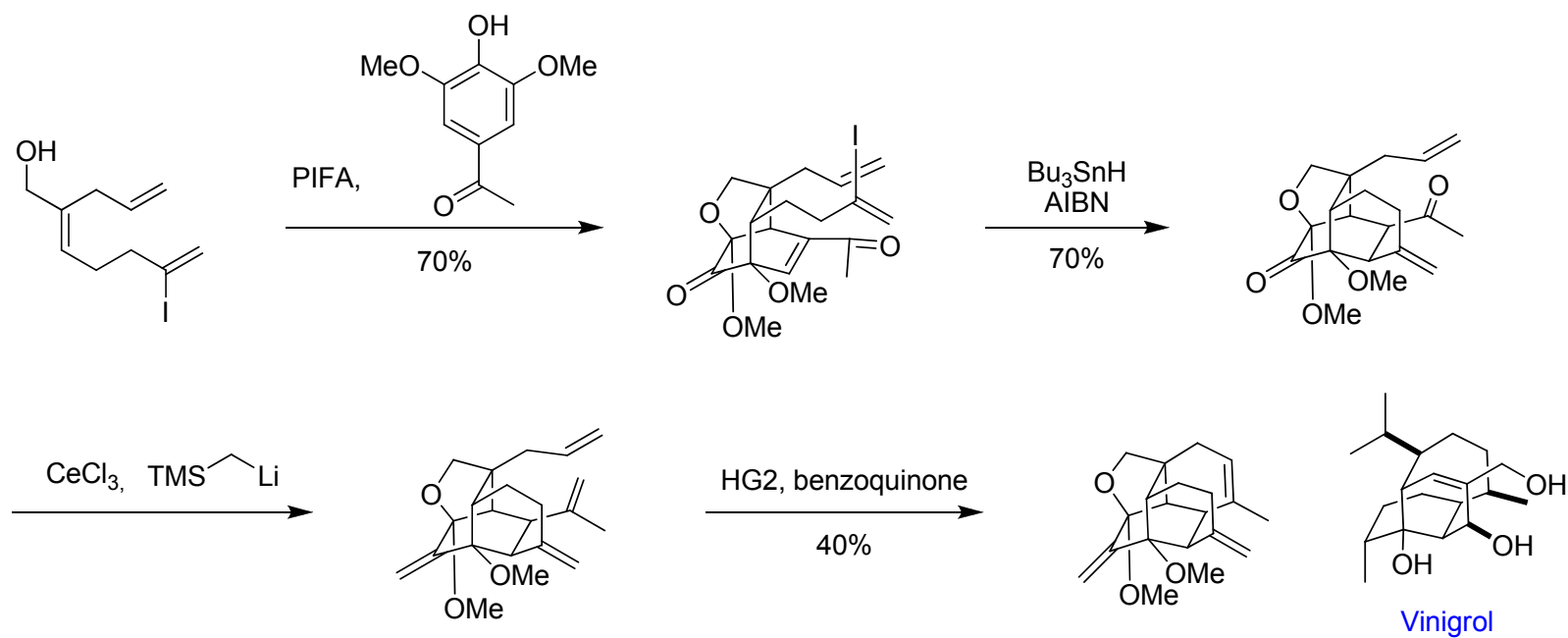
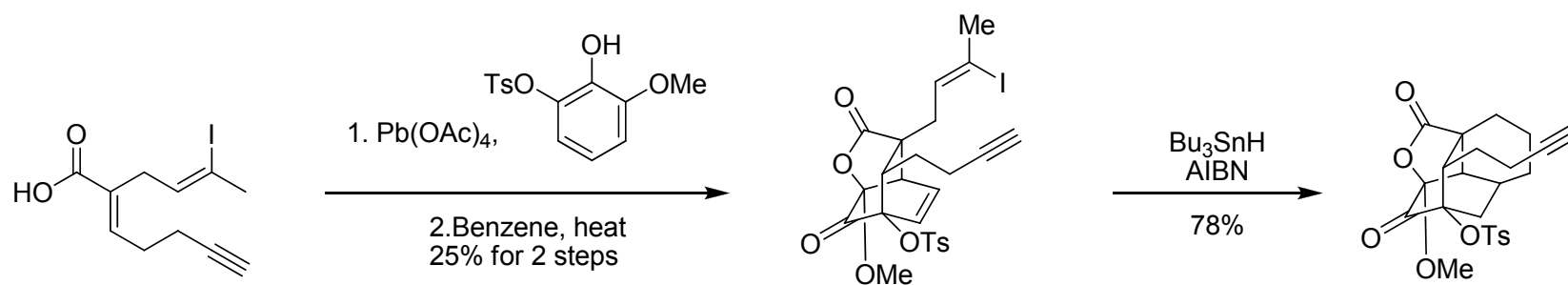
Njardarson's Retrosynthesis



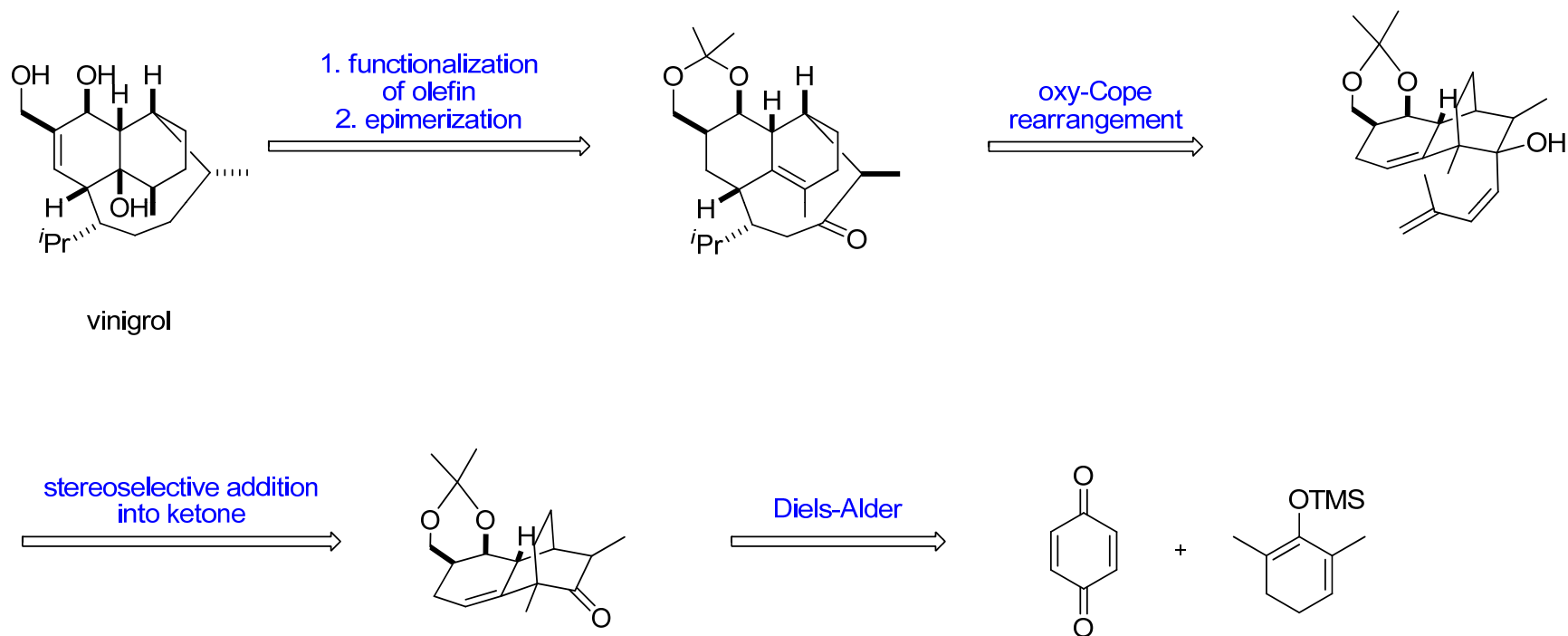
Radical Cascade to Access Vinigrol Core



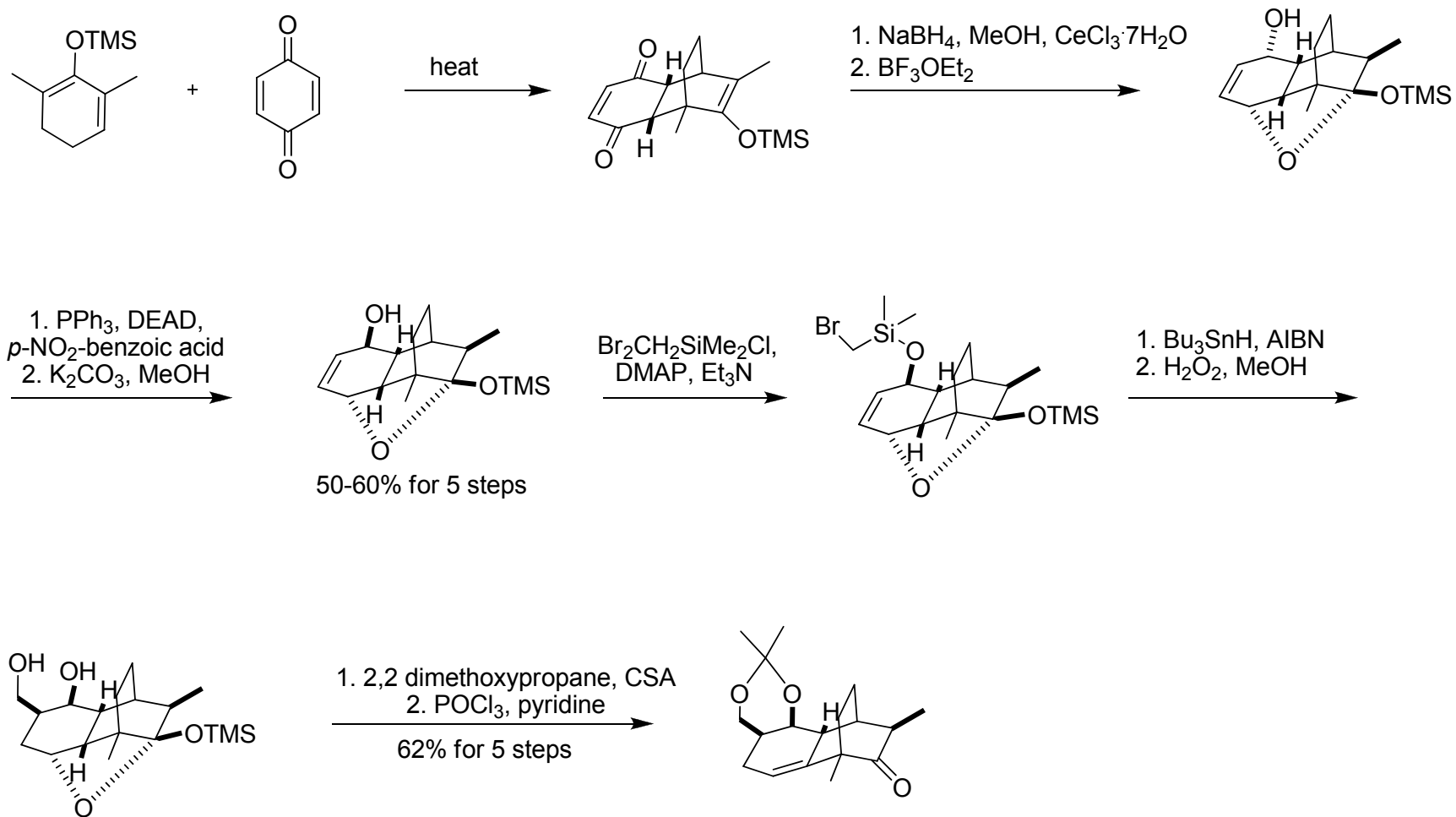
A Stepwise Approach



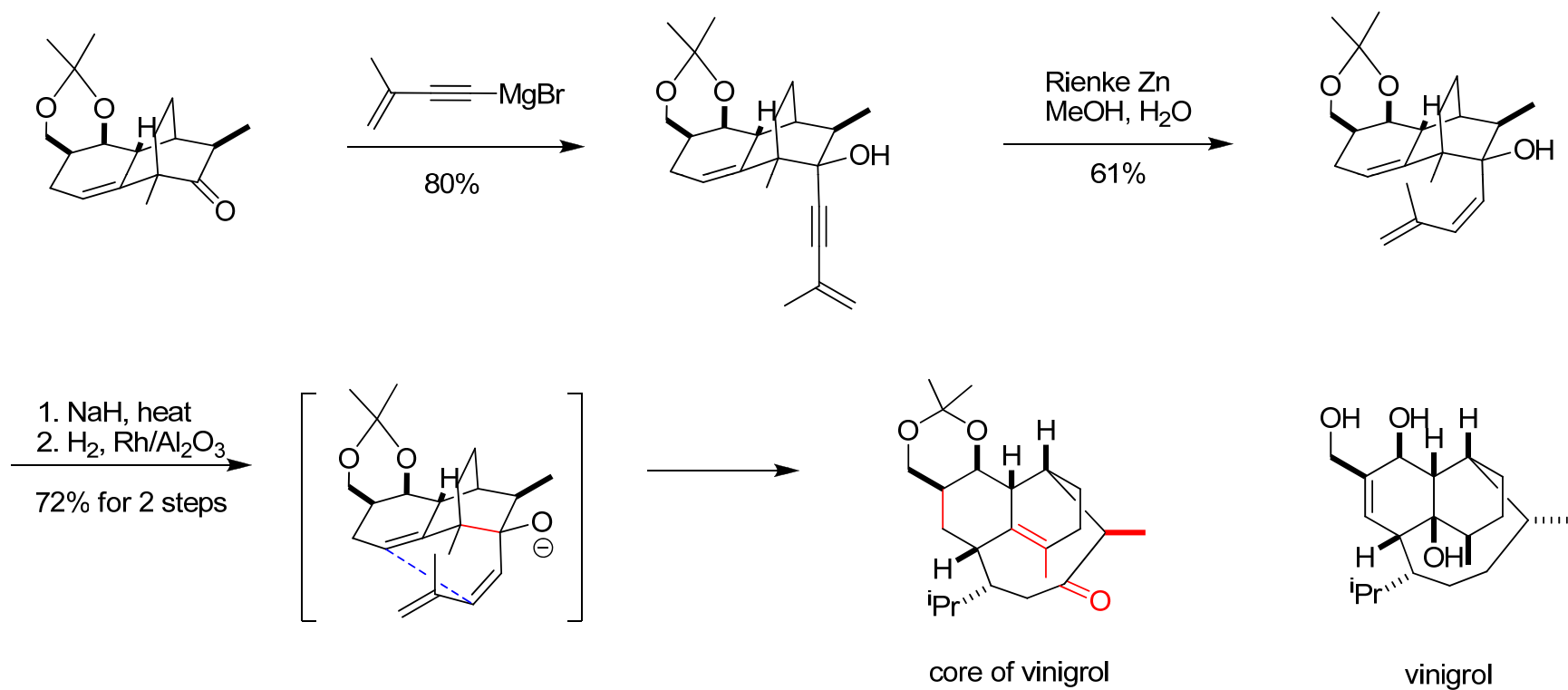
Hanna's Retrosynthesis



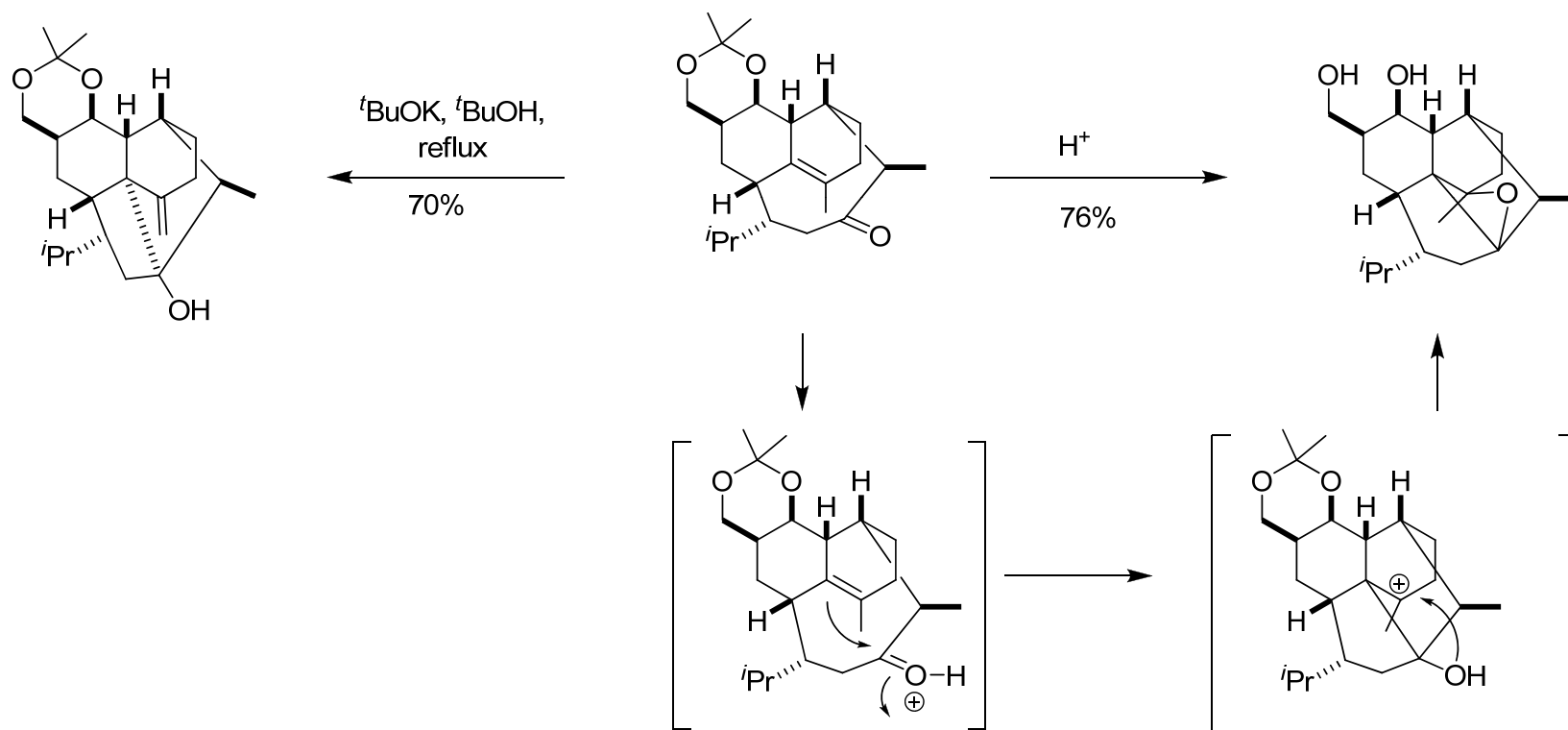
Synthesis of the Oxy Cope Precursor



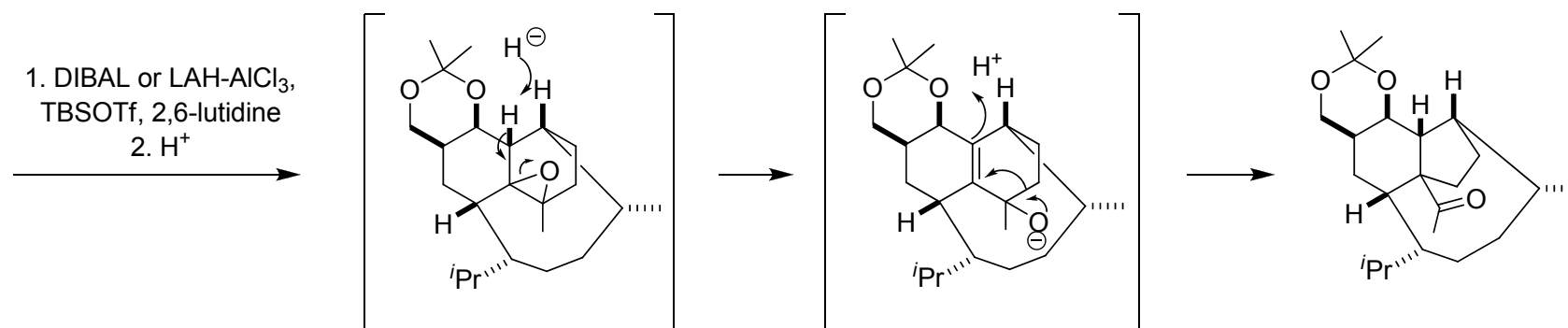
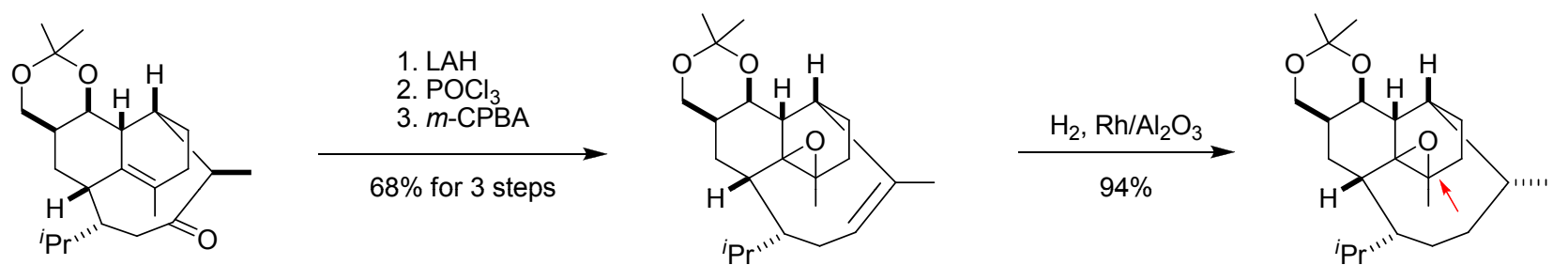
Synthesis of the Core of Vinigrol



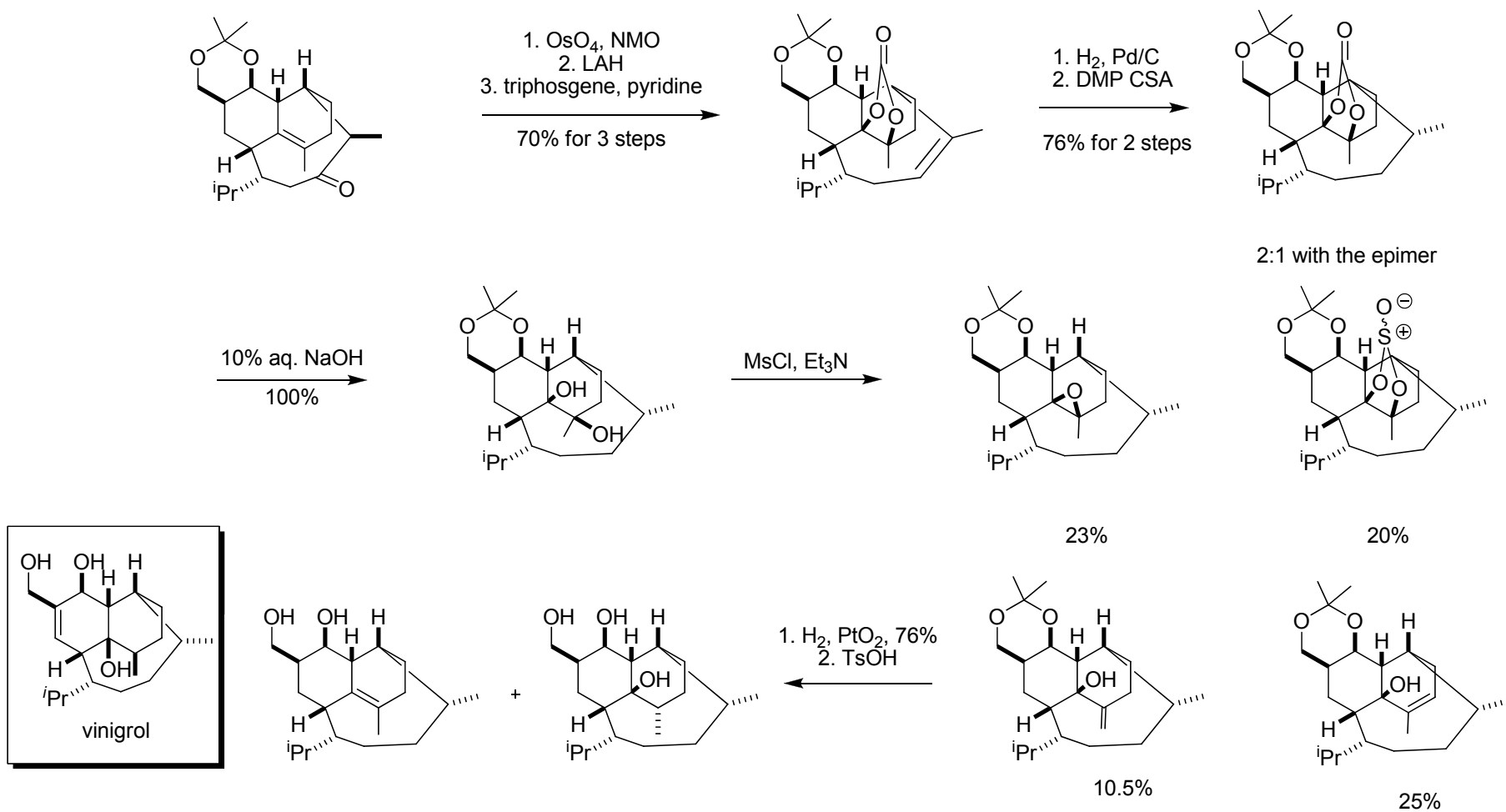
Epimerization Attempts



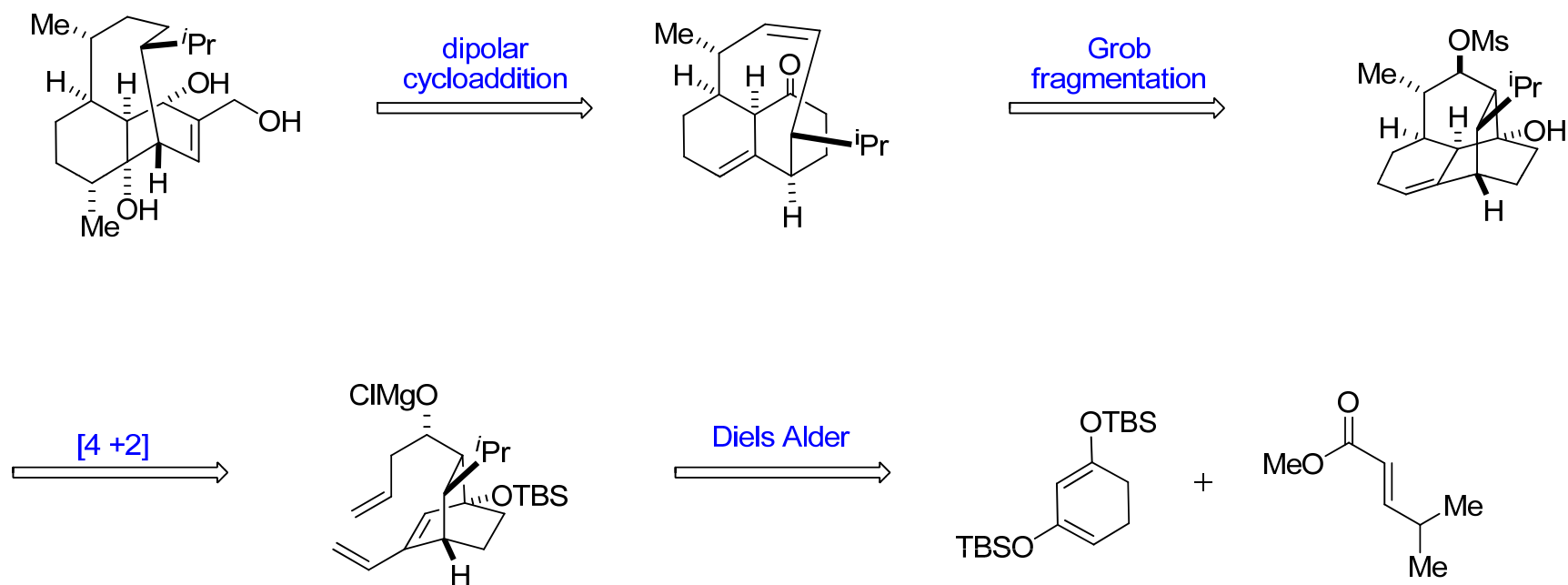
Epimerization Attempts



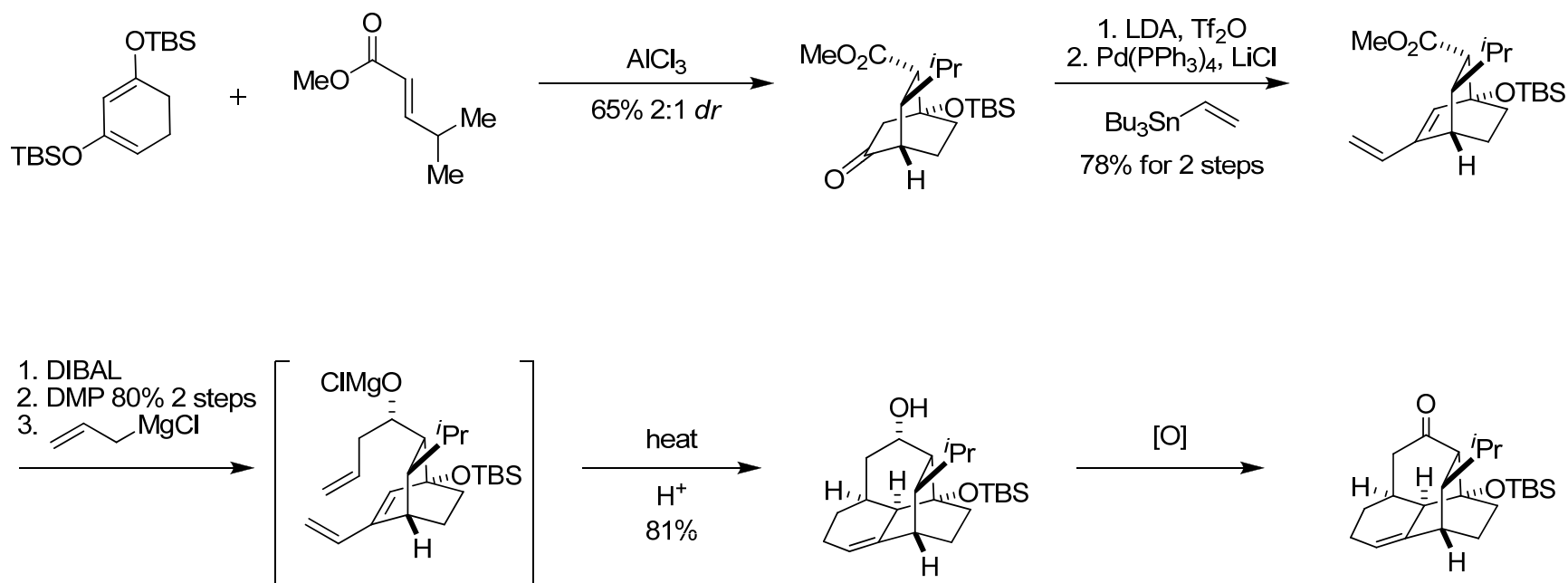
Attempts to Elaborate the Vinigrol Core



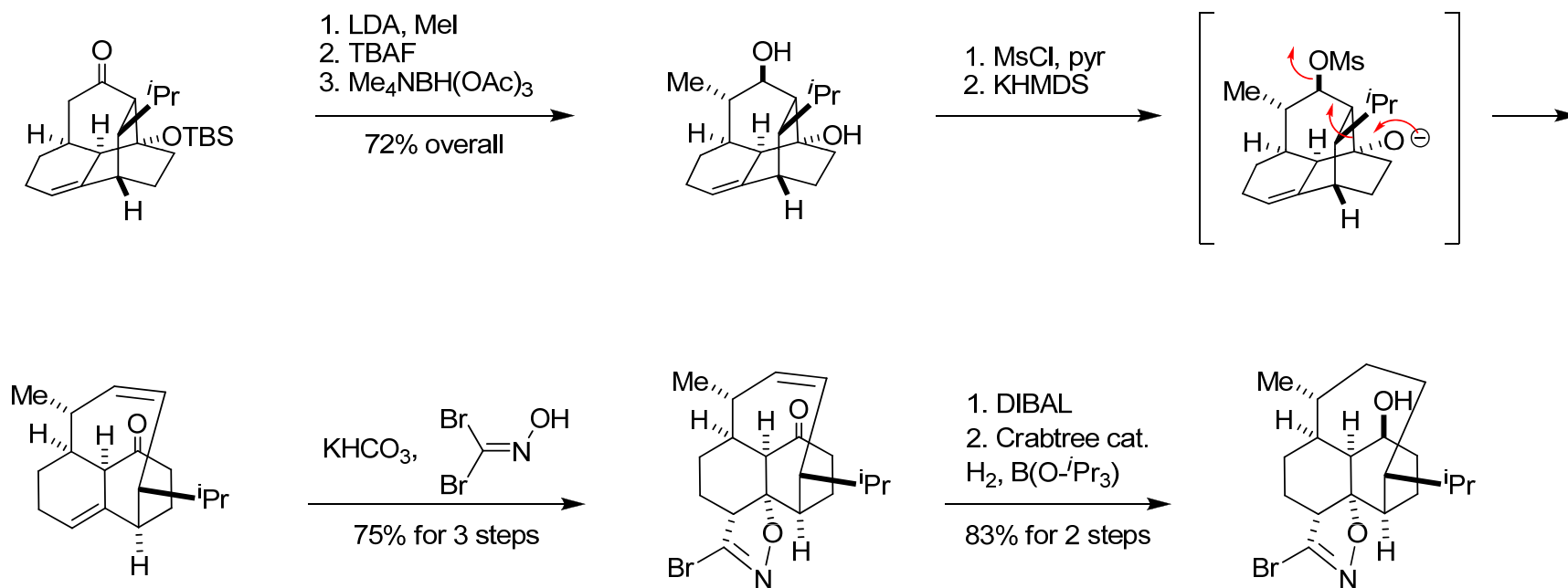
Baran's Retrosynthesis



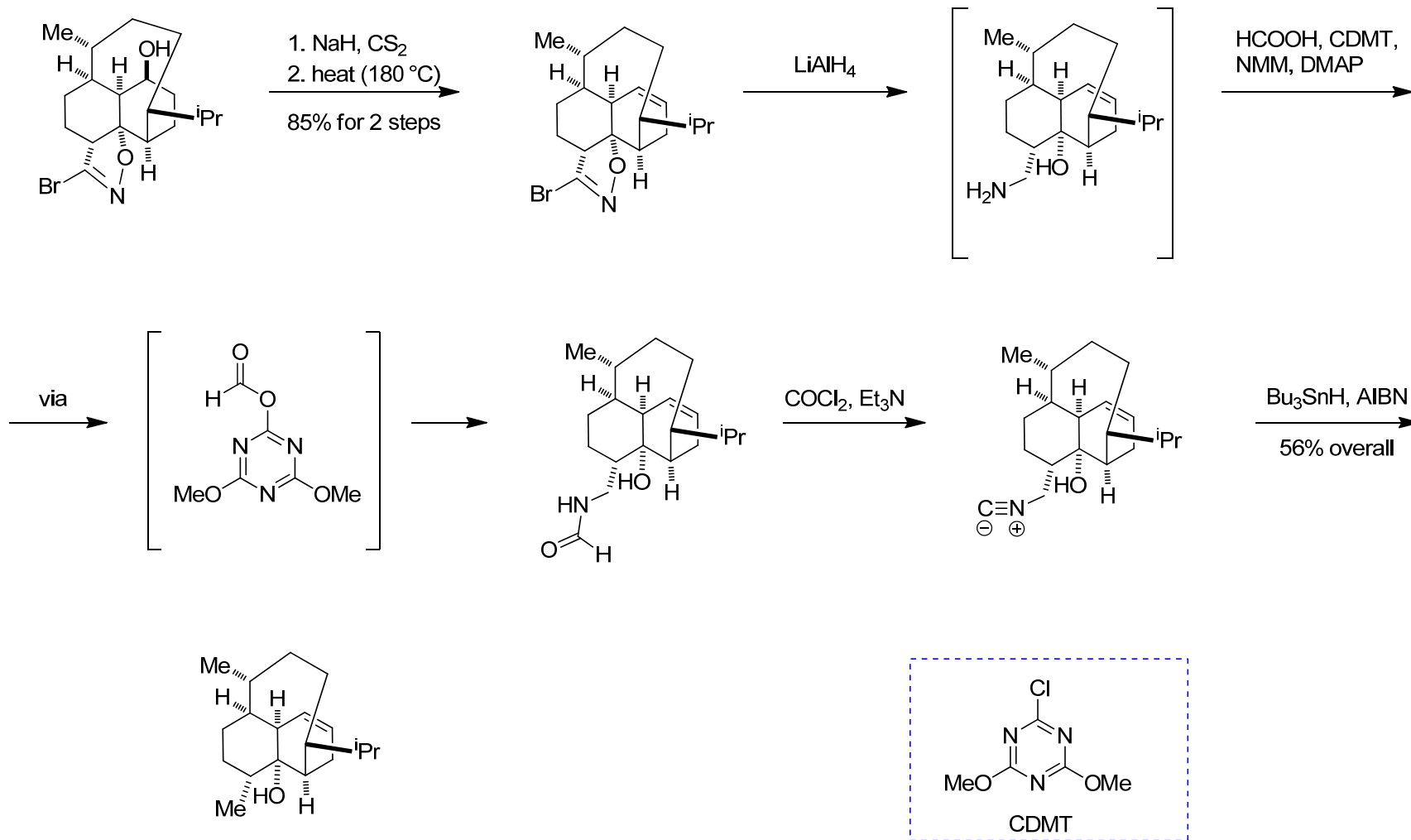
Baran's Total Synthesis of (±)-Vinigrol



Total Synthesis of (±)-Vinigrol

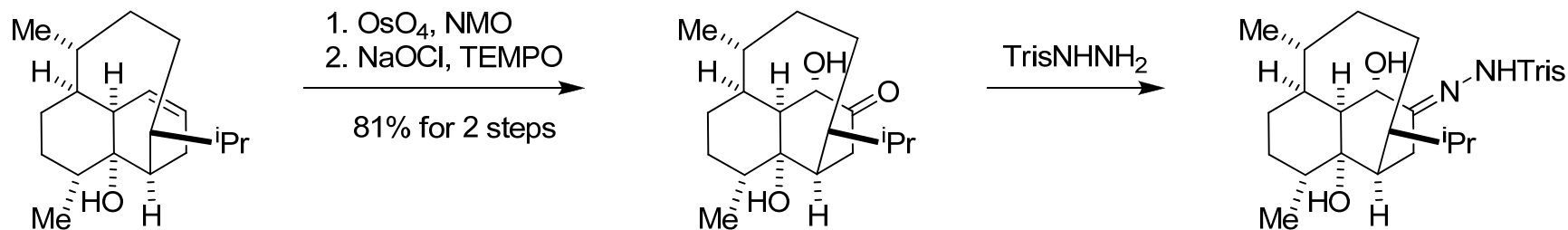


Total Synthesis of (±)-Vinigrol



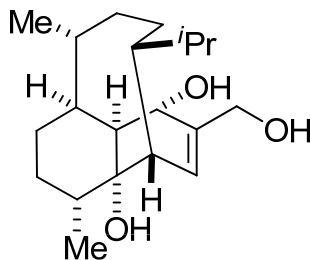
Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 17066.

Total Synthesis of (±)-Vinigrol



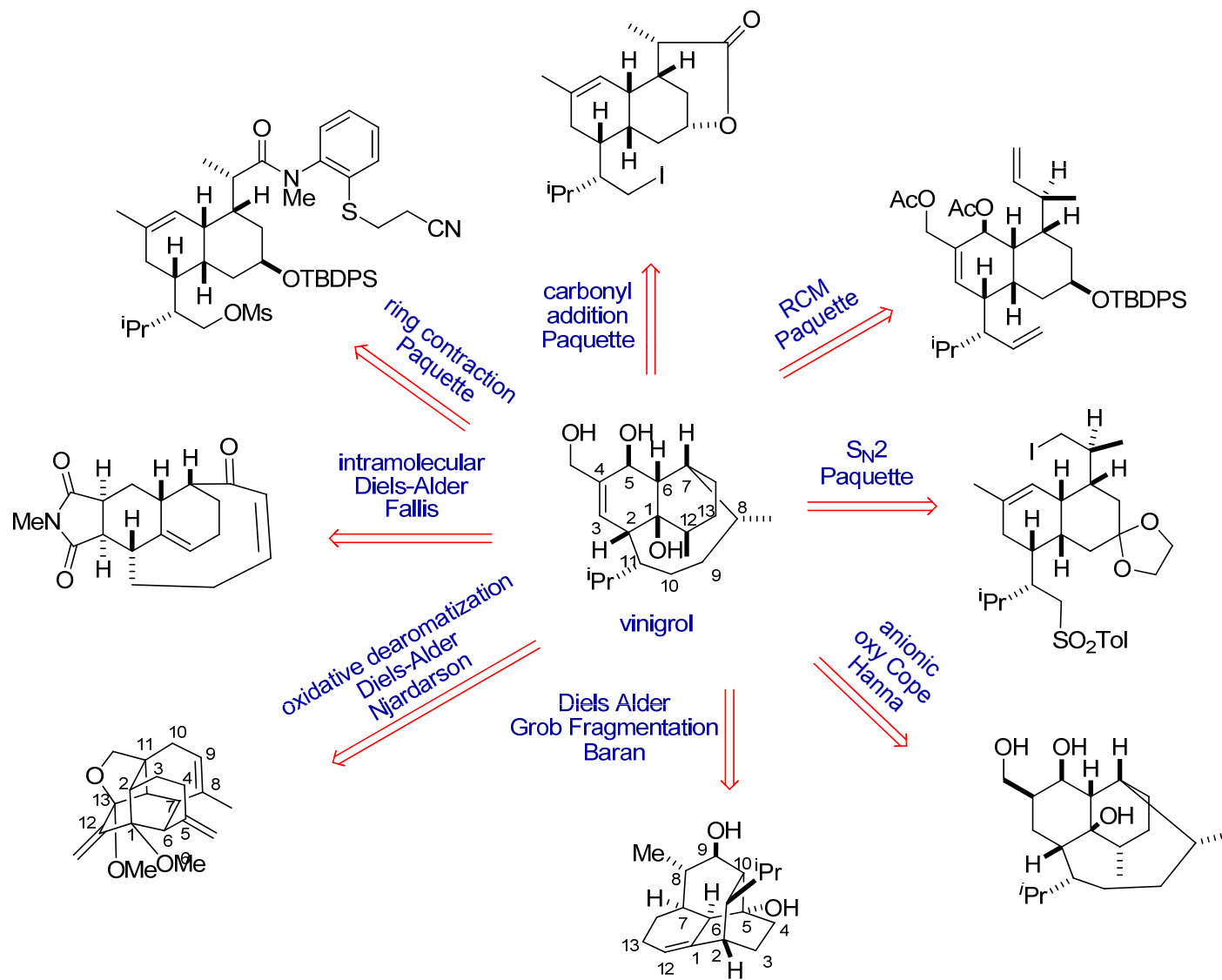
i. $n\text{BuLi}$, TMEDA
ii. $(\text{CH}_2\text{O})_n$

51% overall



Summary:
23 total steps from commercially available material
3% overall yield
2 Diels Alder Reactions
Groß Fragmentation
Dipolar cycloaddition

Summary



adapted from: Lu, J.; Hall, D. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2286.