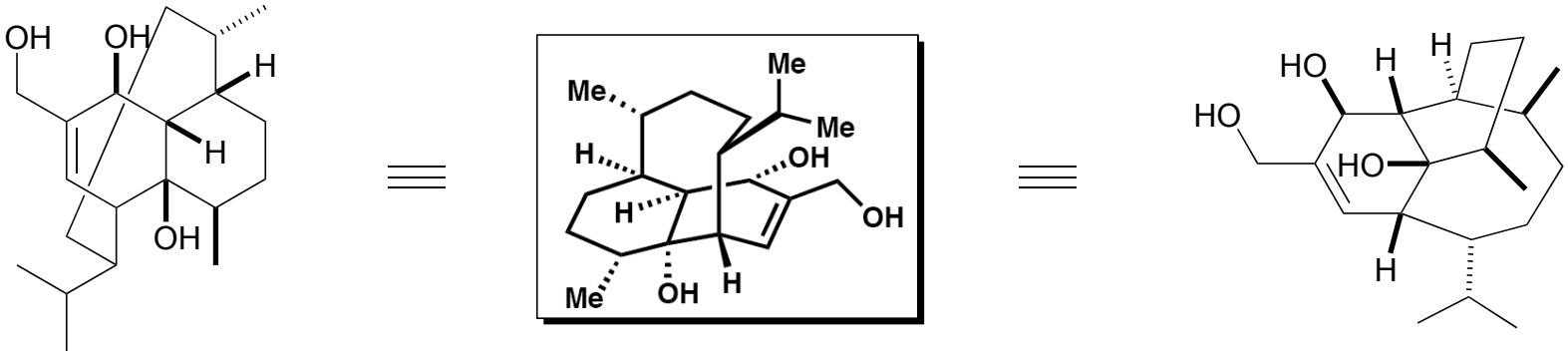
# The Total Synthesis of Vinigrol



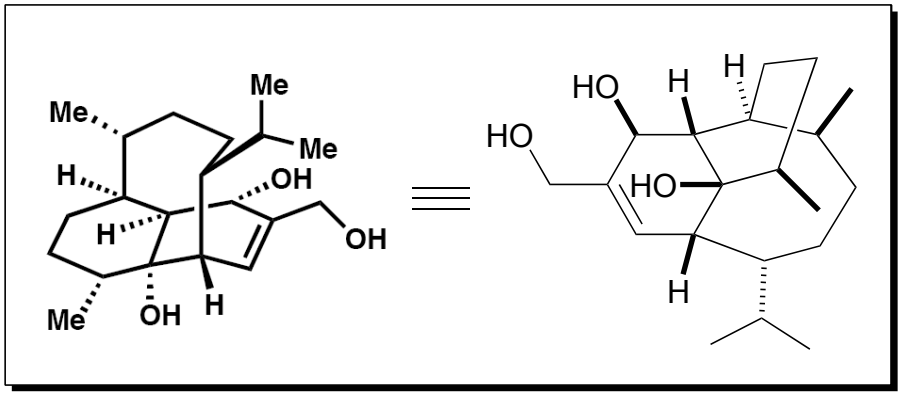

Phil Baran, Thomas J. Maimone, Jun Shi, Shinji Ashida

*J. Am. Chem. Soc.* **2009**, *ASAP*

Current Literature - November 14th, 2009

Nolan Griggs

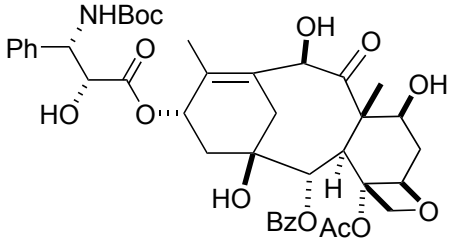
# Vinigrol - Introduction




• Isolated by Ando and co-workers in 1987 from *Virgaria nigra* F-5408, a fungus strain found at the foot of Mount Aso, Japan.

Ando, et al.; *JOC* **1987**, 52, 5292.

• Tricyclic core contains 8 contiguous stereocenters around a bridged *cis*-decalin core.




Docetaxel (Trade name - Taxotere)

• Core structure is similar to that of the taxane family:

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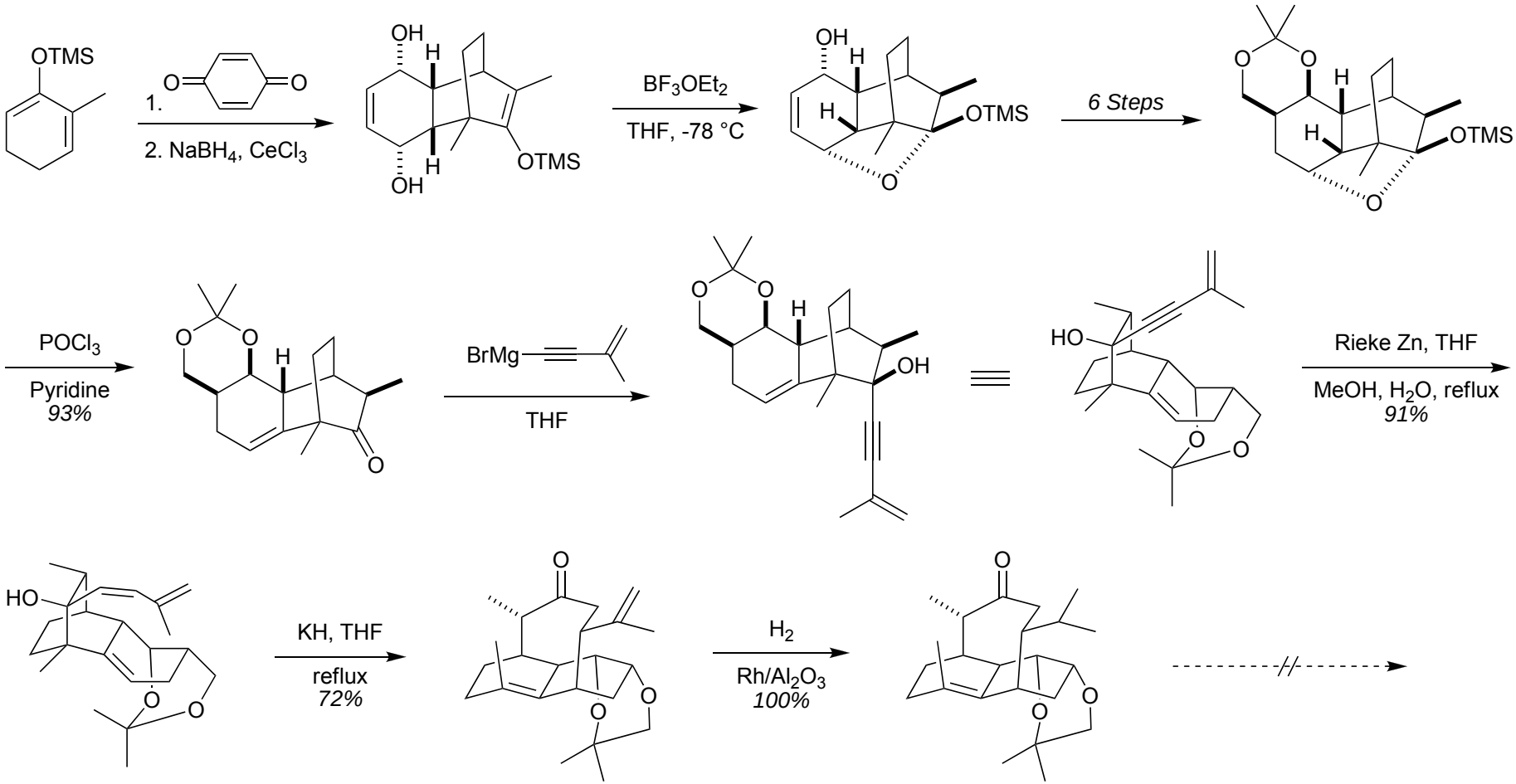
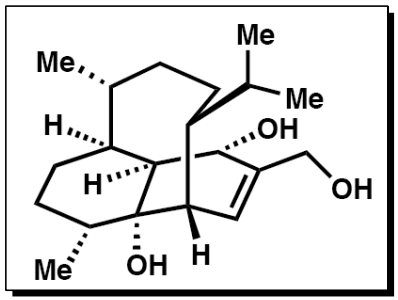
Vinigrol has interesting biological activity including:

- Activity against human platelet aggregation with $IC_{50}$ values ~ 50 nM.
- Identified as a tumor necrosis factor (TNF) antagonist, which is useful in the treatment of AIDS.
- Other antiinflamitory properties and immunosupressant antagonistic effects.

Review: Barriault, Louis, Tessier, Guillaume; *Org. Prep. and Proc.* **2007**, 39(4), 311-353.

# Efforts by Hanna and co-workers

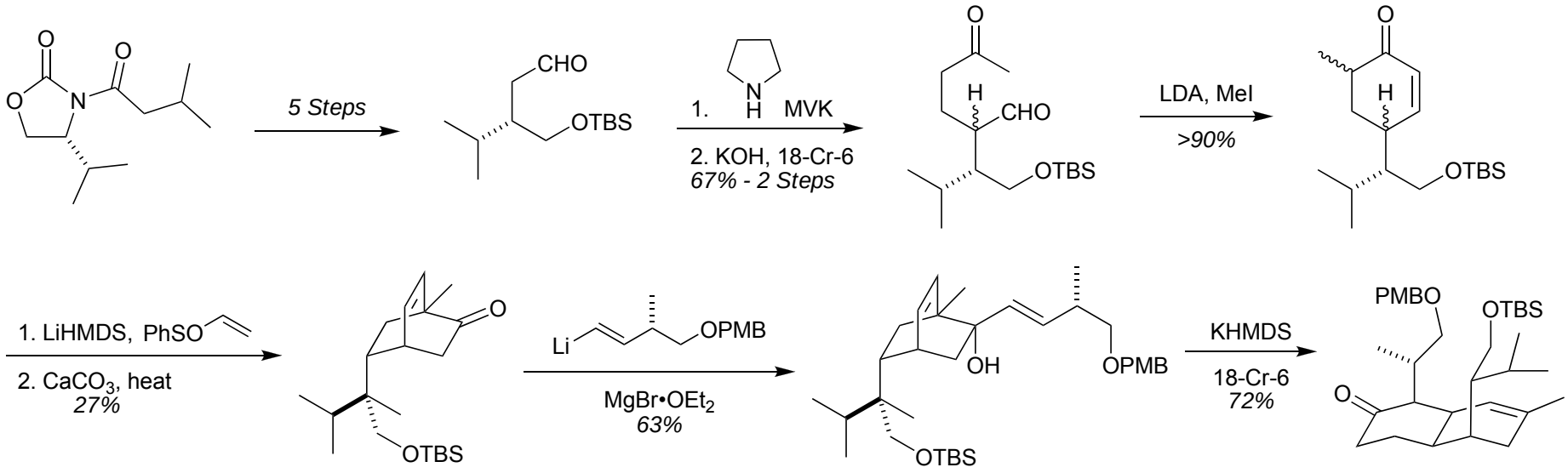




Hanna, I.; Devaux, J.F.; Lallemand, J.Y.; Prange´, T.; *J. Org. Chem.* **1993**, 58, 2349-2350.
Hanna, I.; Devaux, J.F.; Lallemand, J.Y.; *J. Org. Chem*. **1997**, 62, 5062-5068.
Hanna, I., Gentric,L., Ricard, L.; *Org. Lett.* **2003**, 5(7), 1139-1142.

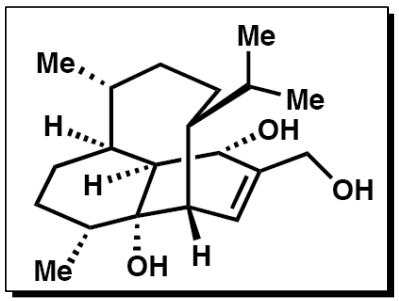
# Efforts by Paquette and co-workers




All attempts to close the 8-membered ring failed. Among the different methods used are:

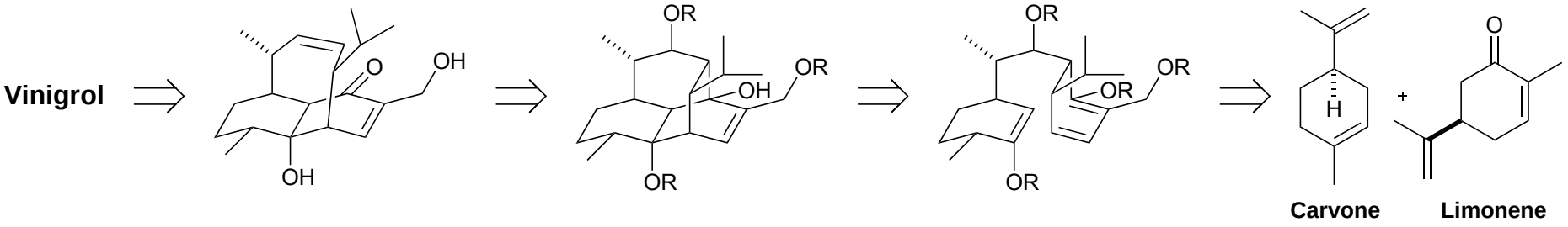
- Ring Closing Metathesis on many different variants of *cis*-decalin precursor.
- Barbier-type ring closures
- Variants of the McMurry Reaction
- Ring contraction strategies involving examples such as a Ramberg-Backlund Rearrangement

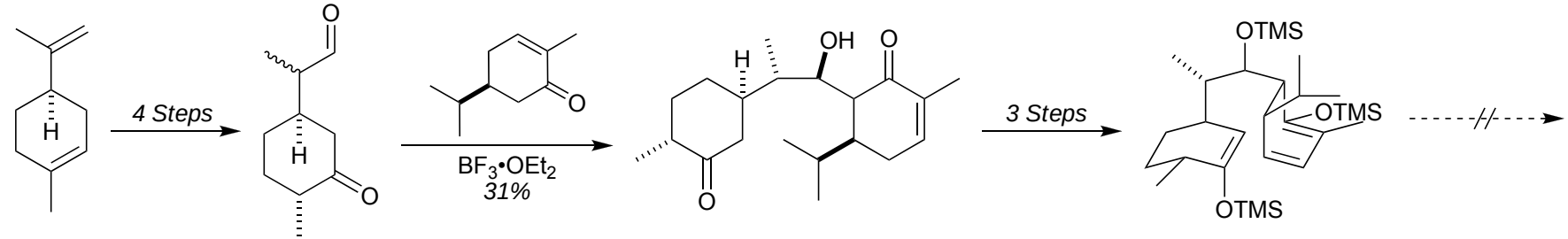
- As a result, it was concluded that this strategy was not useful due to the equatorial nature of the sidechains, and therefore, no further attepts have been made.

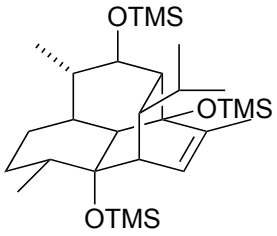


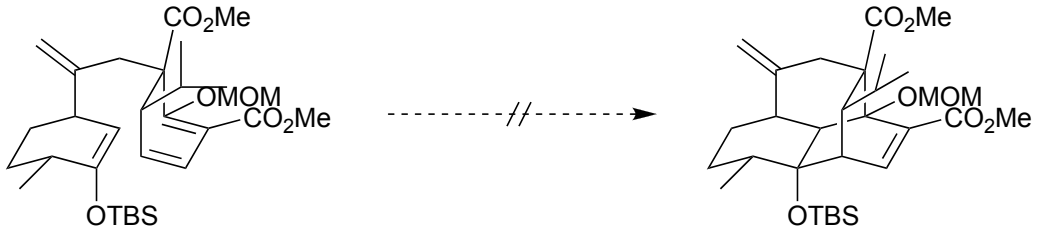

Efremov, I. V. Ph.D. Thesis, The Ohio State University, 2001
Paquette, L. A., Guevel, R., Sakamoto, S., Kim, I. H., Crawford, J.; *J. Org. Chem.* **2003**, 68, 6096–6107.
Paquette, L. A., Efremov, I., Liu, Z. S.; *J. Org. Chem.* **2005**, 70, 505–509.
Paquette, L. A., Efremov, I.; *J. Org. Chem.* **2005**, 70, 510–513.
Paquette, L. A., Liu, Z. S., Efremov, I.; *J. Org. Chem.* **2005**, 70, 514–518.

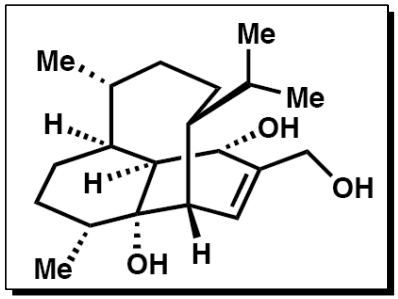
# Efforts by Corey and co-workers



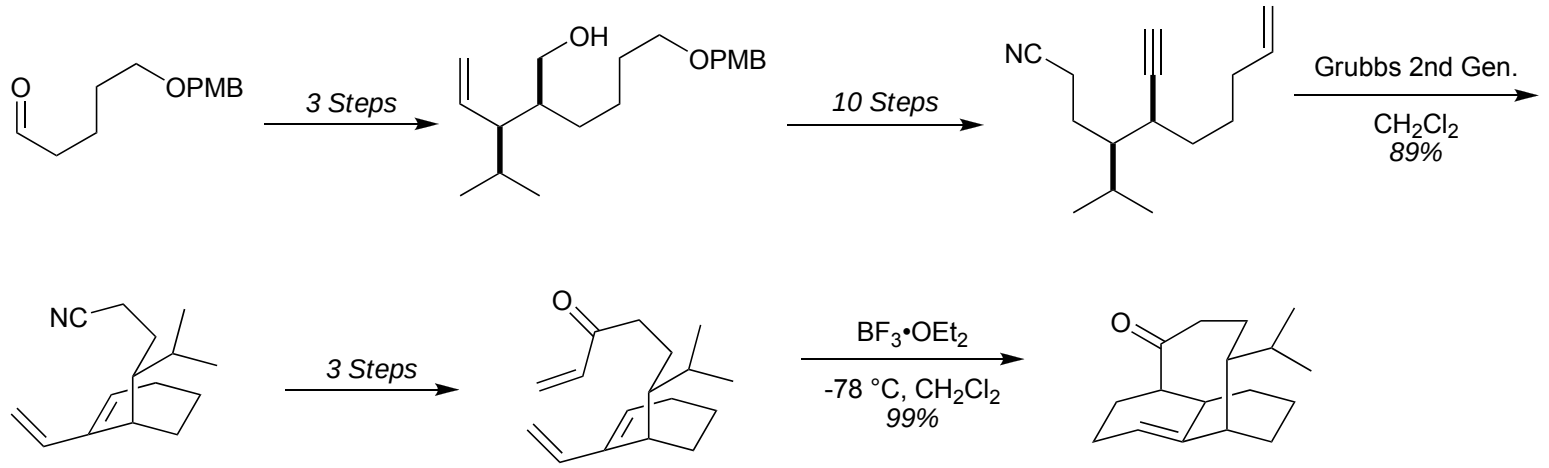



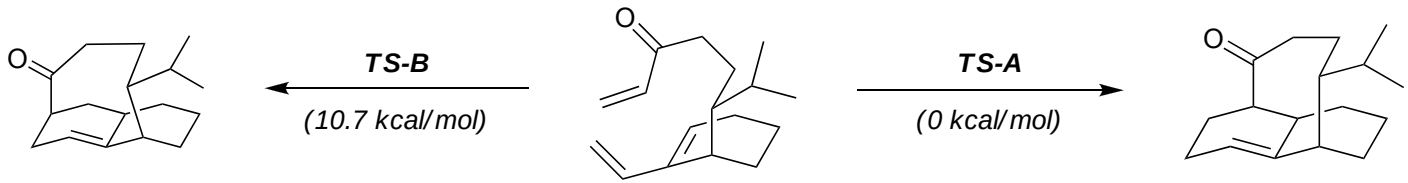



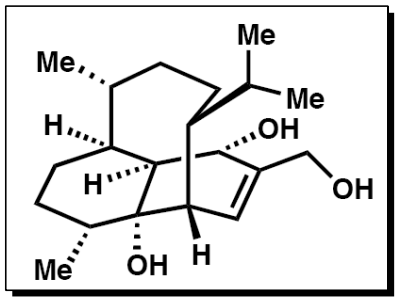

Goodman, S. N.; Ph.D. Thesis; Harvard University, **2000**

# Efforts by Barriault and co-workers




- DFT Calculations of gas-phase relative free energies at 298 K at the B3LYP level using 6-31G** basis set.

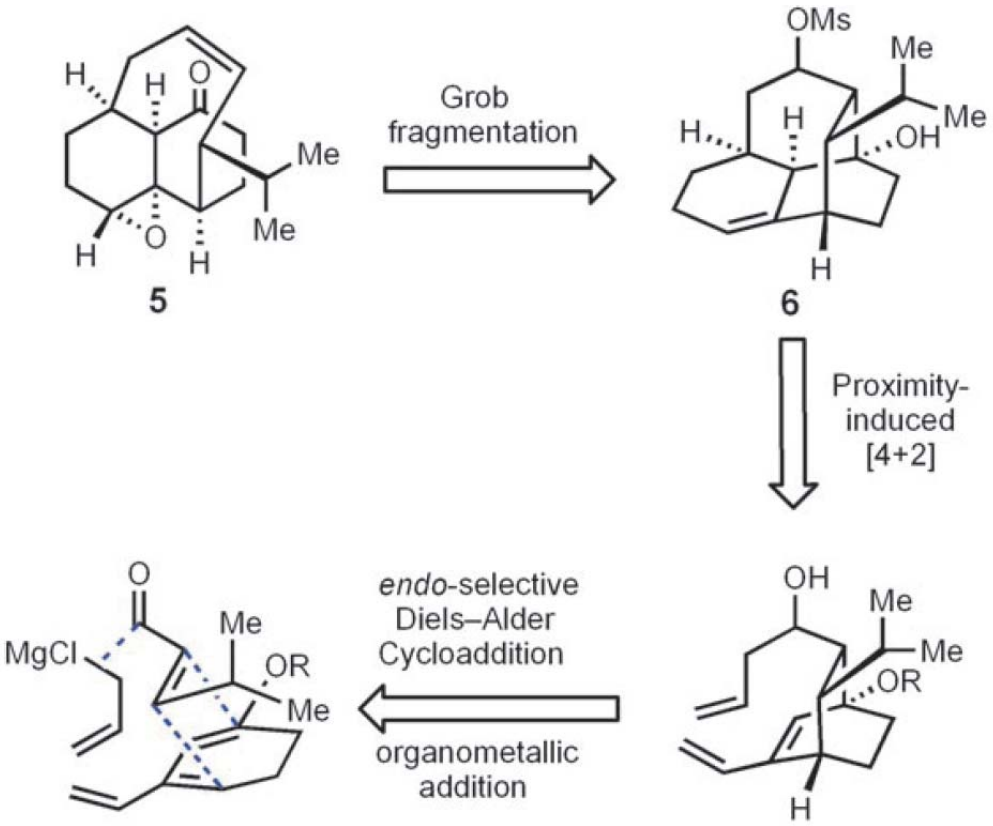


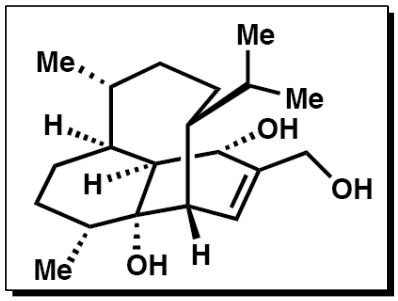

Barriault, Louis, Brise, C.M., Tessier, G.; *Org. Lett.* **2007**, 9(8), 1545-1548.

For other approaches by the same lab, see:
Barriault, Louis, Morency, L.; *J. Org. Chem.* **2005**, 70, 8841.
Barriault, Louis, Morency, L.; *Tetrahedron Lett.* **2004**, 45, 6105.

A similar strategy was disclosed later that year by Fallis and co-workers:
Fallis, A.G., Souweha, M.S., Enright, G.D.; *Org. Lett.* **2007**, 9(25), 5163-5166.

# Initial Work Towards Vinigrol - Baran and co-workers



Baran, P.S., Maimone, T.J., Voica, A.F.; *Angew Chem. Int. Ed.* **2008**, 47, 3054-3056

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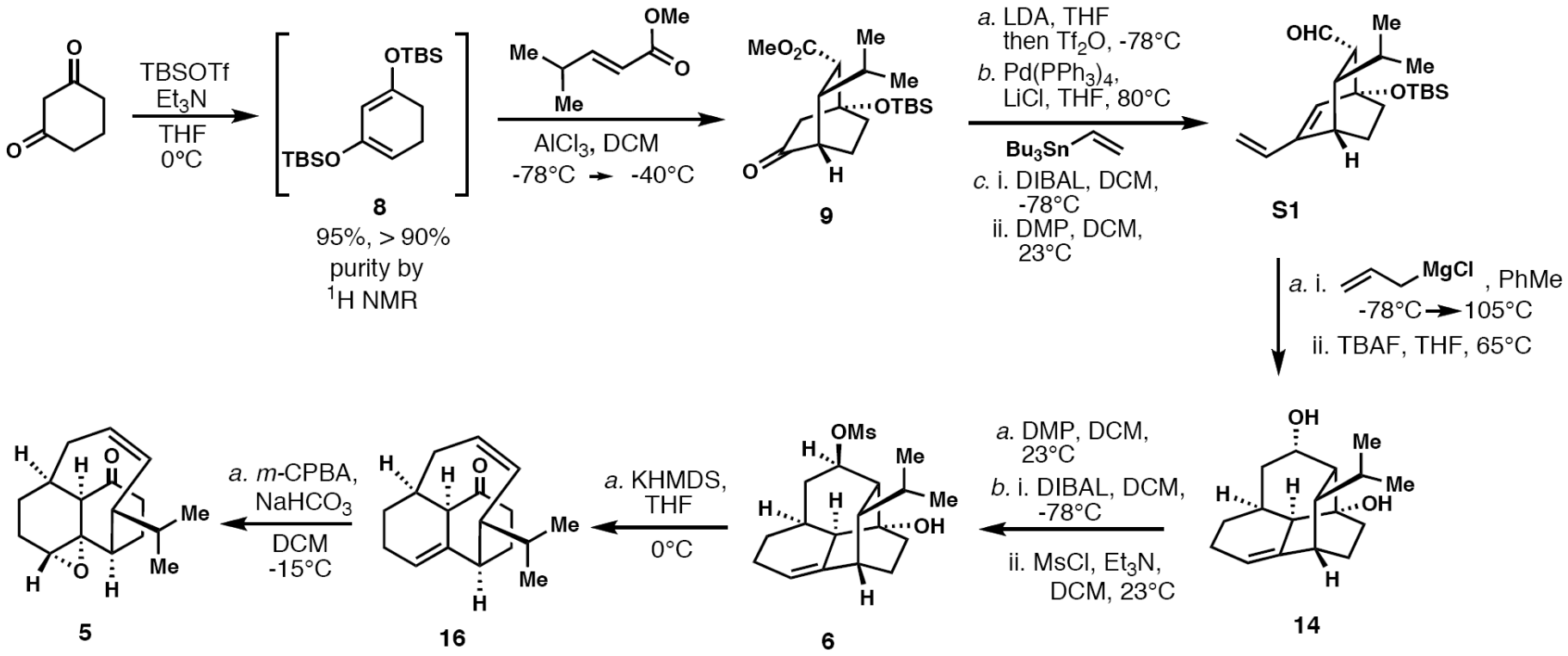
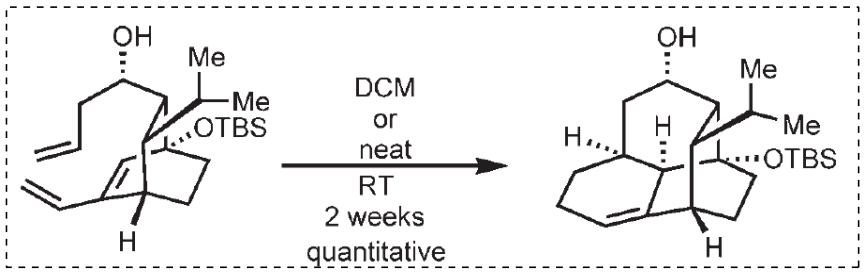
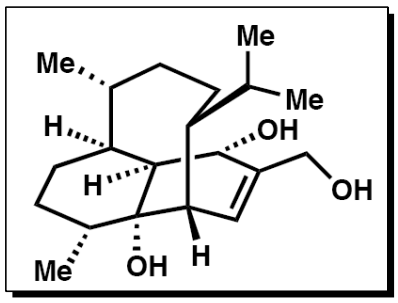
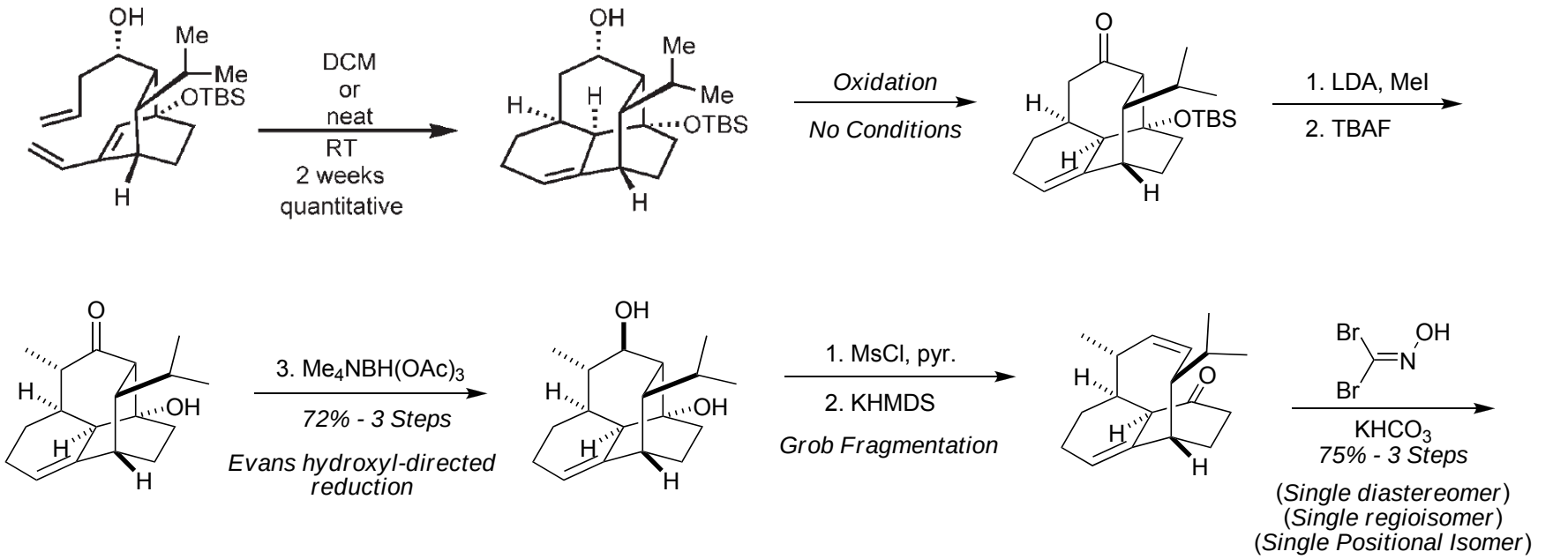



Baran, P.S., Maimone, T.J., Voica, A.F.; *Angew Chem. Int. Ed.* **2008**, 47, 3054-3056

# Completion of the Synthesis of Vinigrol - Baran and co-workers

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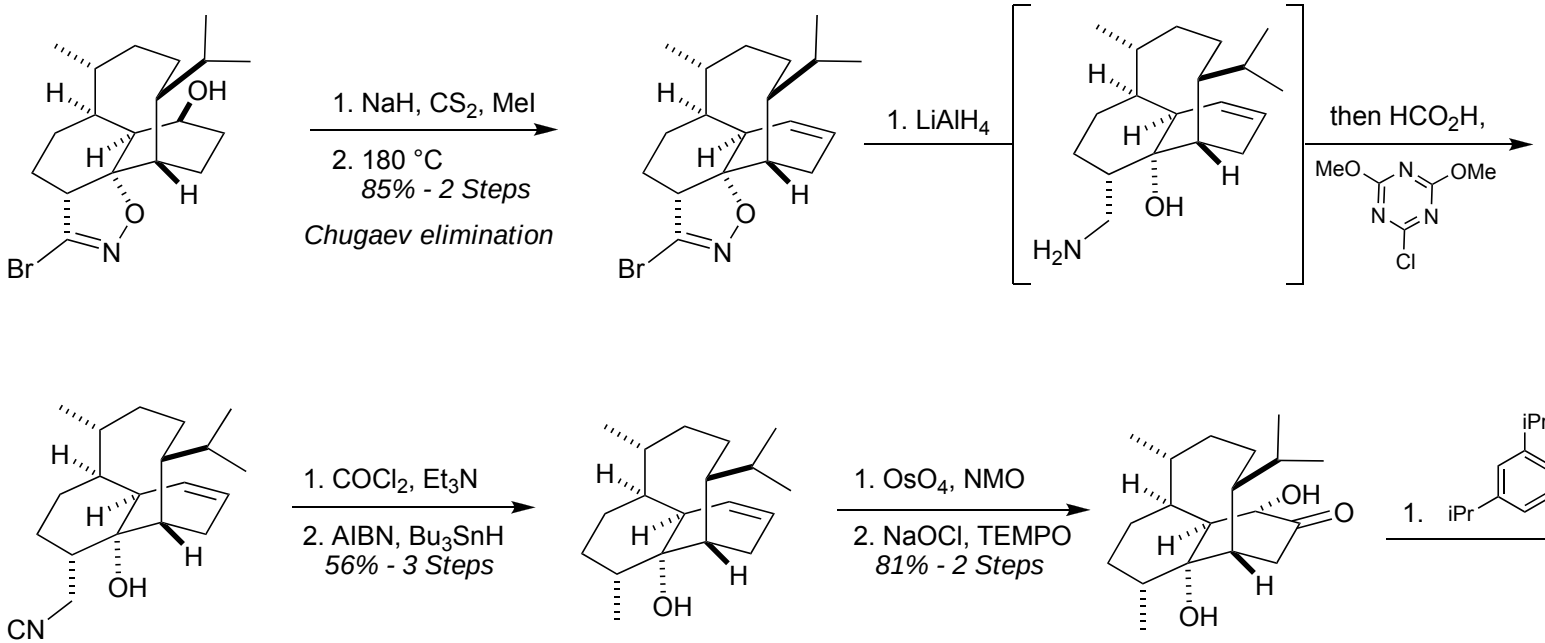
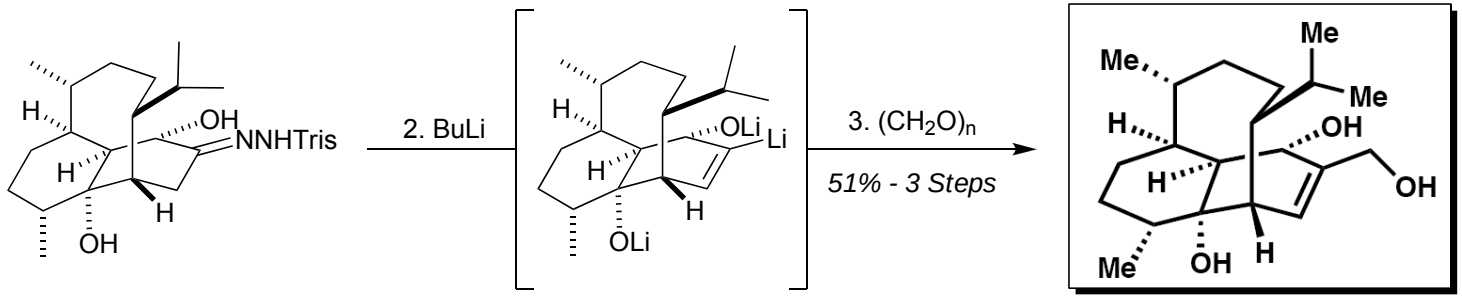



Saegusa, T., et al. *J. Am. Chem. Soc.* **1968**, 90, 4182




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

# Conclusions

- The first total synthesis of Vinigrol was accomplished in 23 steps with an overall yield of 3%
- The synthesis features a minimal use of protecting groups.
- Highlights include facile construction of the core utilizing an electon-neutral intramoleculat Diels Alder reaction and subsequent Grob fragmentation, selective functionalization using an "unusual" dipolar cycloaddition, and a late stage Shapiro reaction.
- Despite the very concise, scaleable route, Baran states "obvious area for refinement" as "a minimalization of nonstrategic redox fluctuations and an enantioselective variant of the first step."