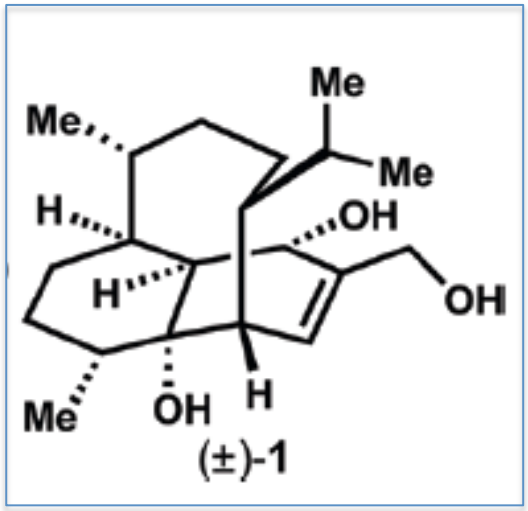
Total Synthesis of Vinigrol



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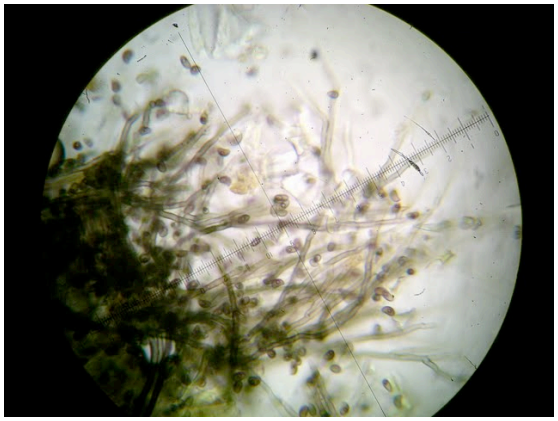
J. Am. Chem. Soc., Article ASAP

Group Meeting Presentation
The Wulff Group
Anil Kumar Gupta
November 20, 2009

Isolation and Biological Activity



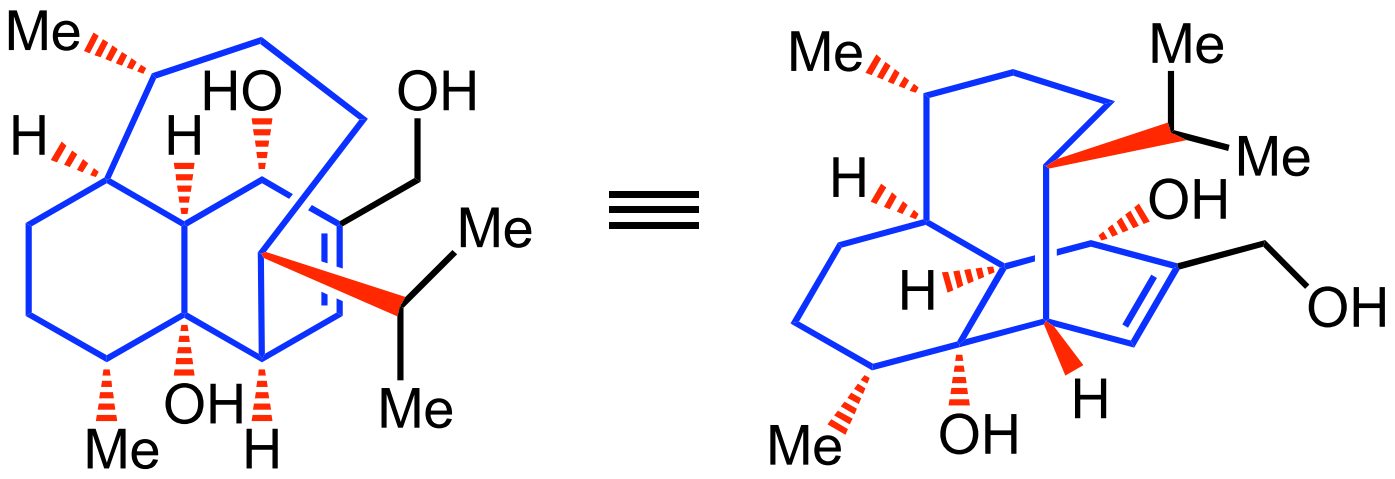
- Vinigrol is a novel diterpenoid isolated from the fungal strain *Virgaria nigra* F-5408.
- The structure has been determined by using chemical derivatizations, spectroscopic measurements, and an X-ray crystal analysis.

- Inhibits platelet activating factor (PAF)-induced platelet aggregation in human plasma with an IC_{50} = 33 nM
- Antihypertensive
- TNF Antagonist

T. Ando, Y. T., N. Ohata, I. Uchida, K. Yoshida, M.; Okuhara, M. *J. Antibiot.* **1988***, 41,* 25-30.

Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *JOC* **1987***, 52,* 5292-5293.

Architectural features and Previous Approaches



A unique decahydro-1,5-butanonaphthalene carbon skeleton

Eight contiguous stereocenters

Multiple sites of oxygenation

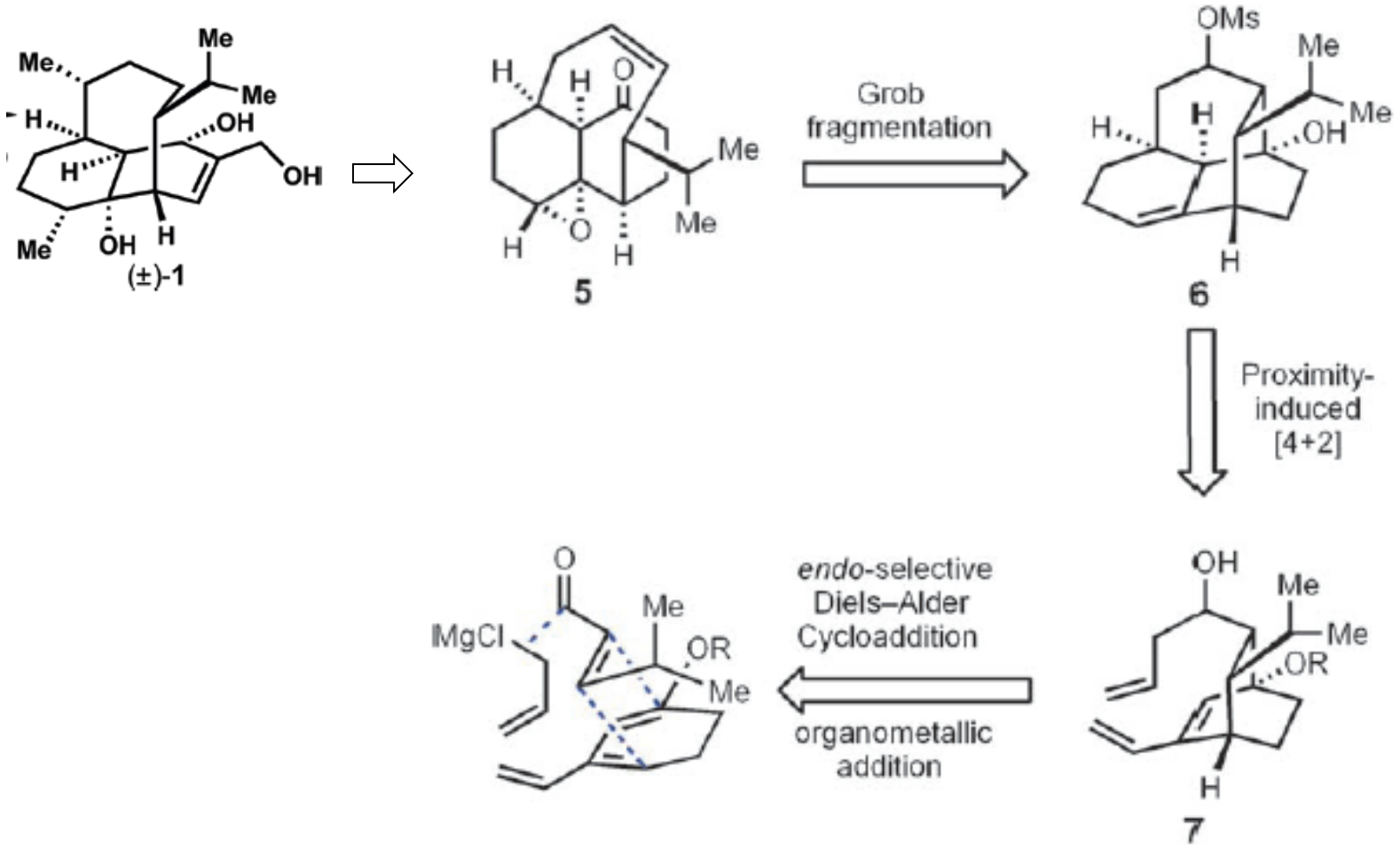
So far:

27 publications
5 dissertations
0 total syntheses

Names Involved:

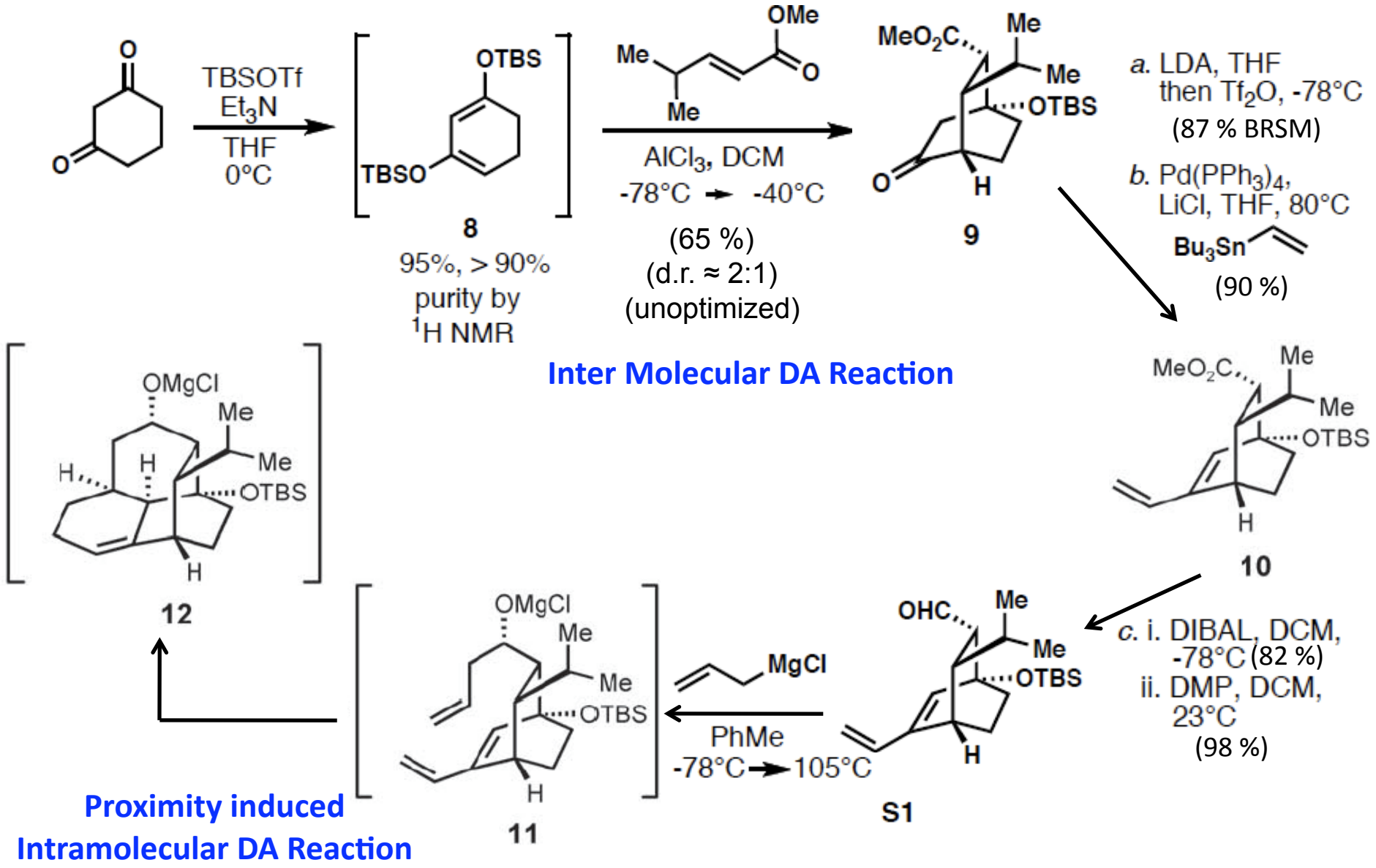
Leo Paquette, E. J. Corey, L. Barriault and many others

Baran's Approach: Retrosynthesis



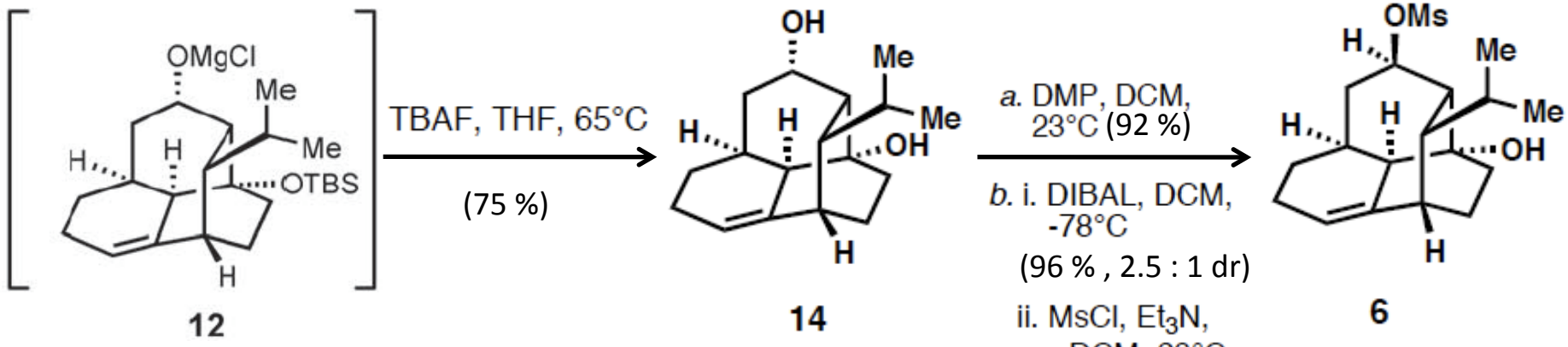
Maimone, T. J.; Voica, A.-F.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47,* 3054–3056.

Synthesis of Fragment 16



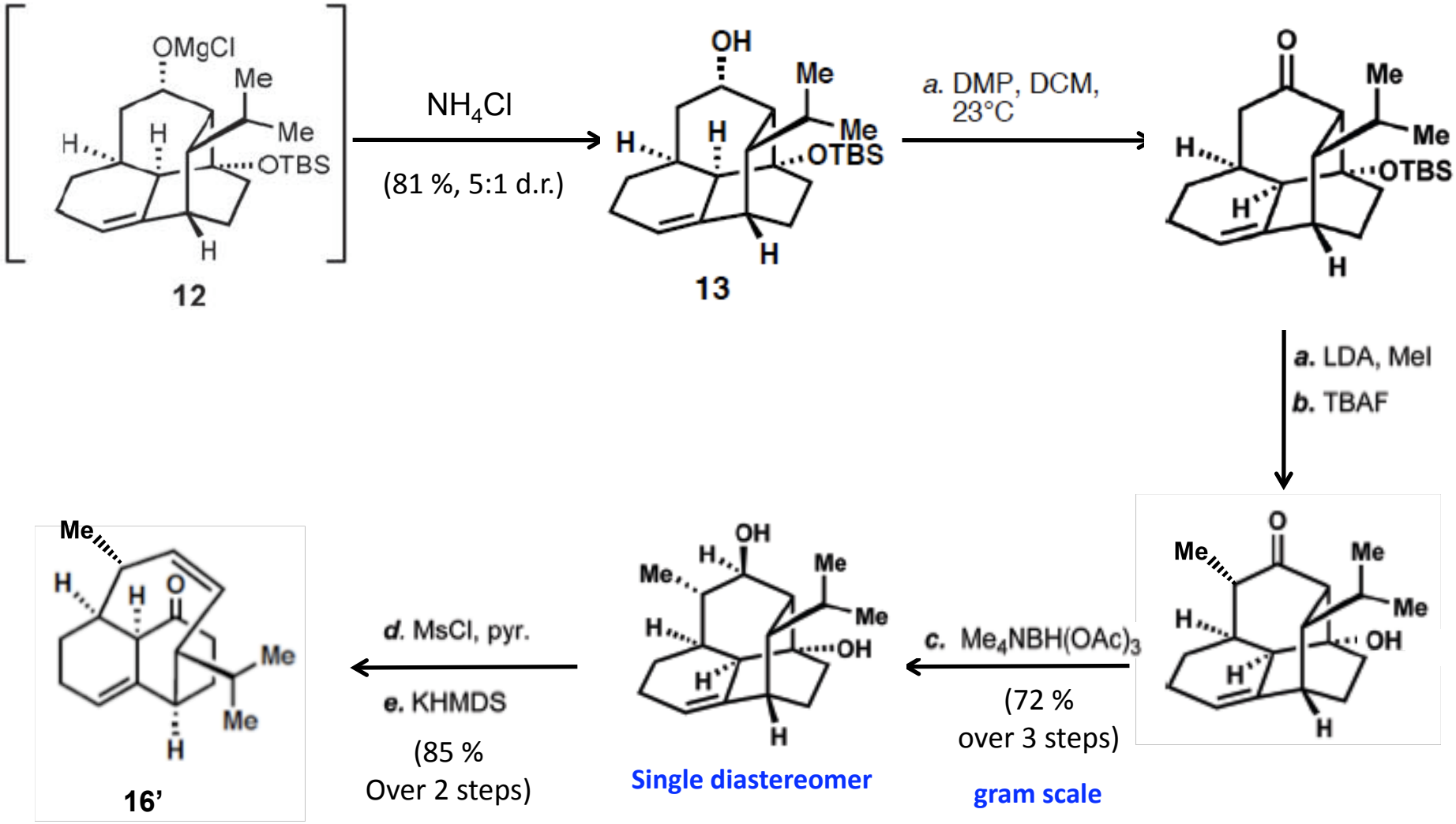
Maimone, T. J.; Voica, A.-F.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47,* 3054–3056.

Synthesis of Fragment 16



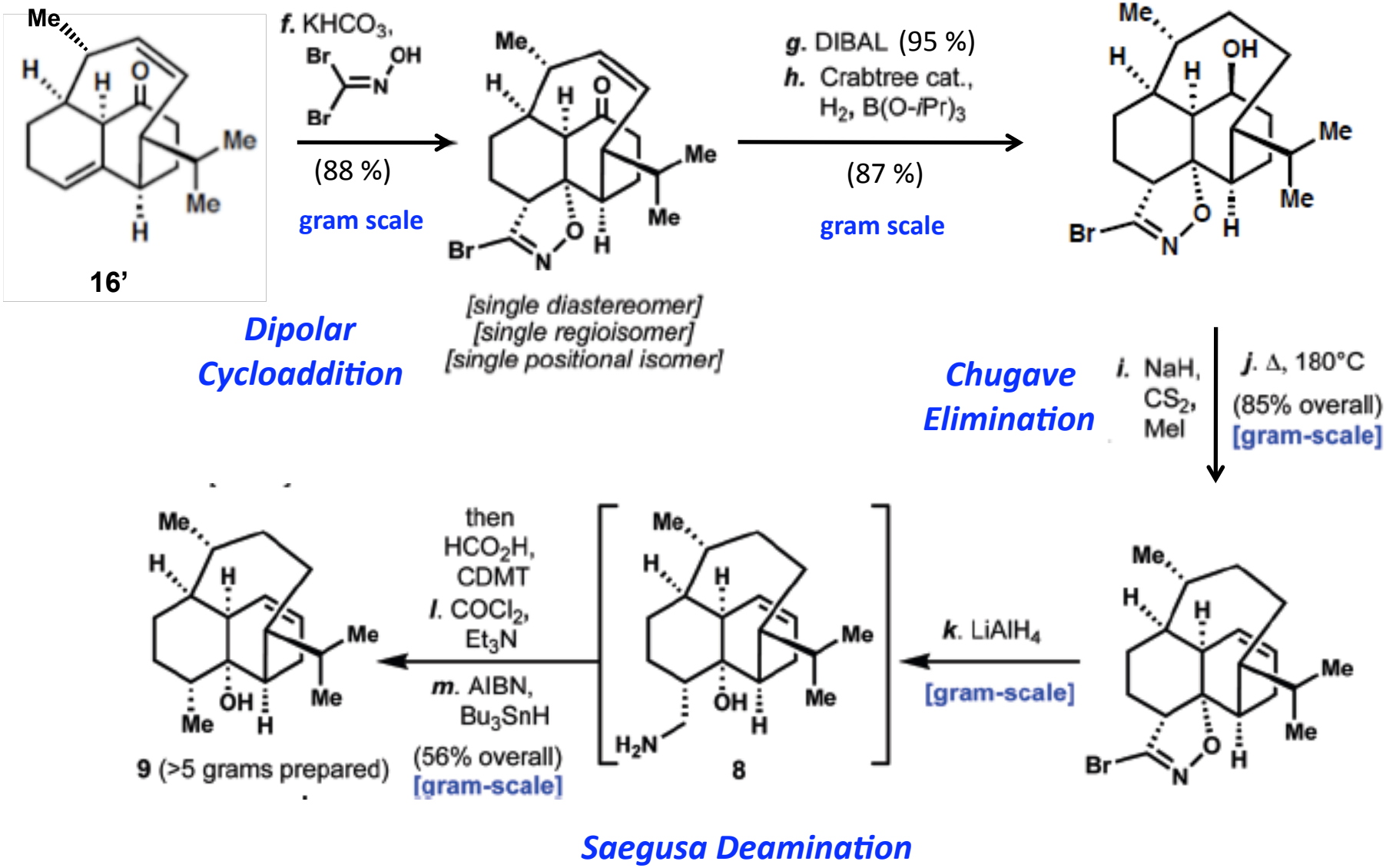
Maimone, T. J.; Voica, A.-F.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47,* 3054–3056.

Synthesis of Fragment 16'

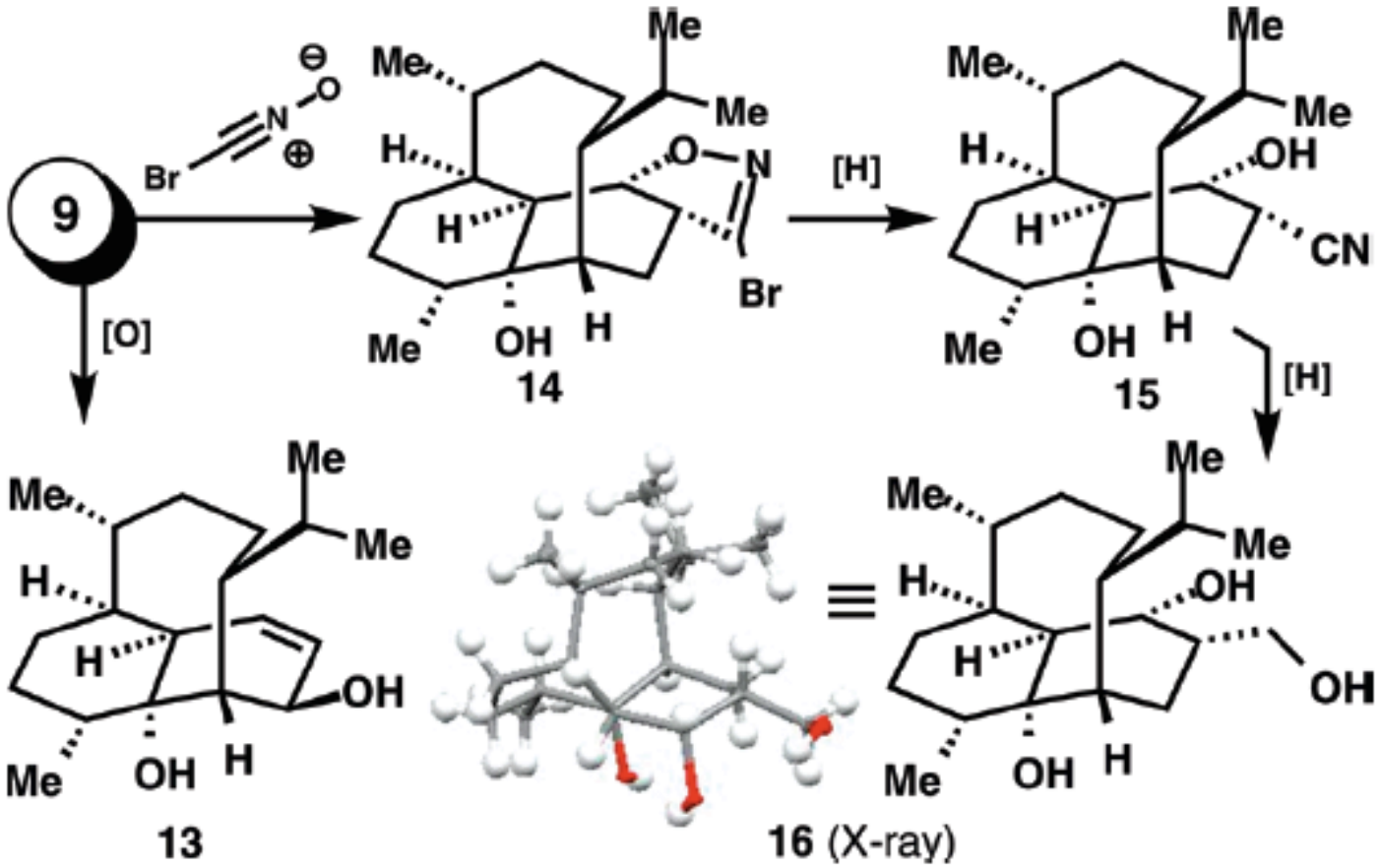


GROB FRAGMENTATION

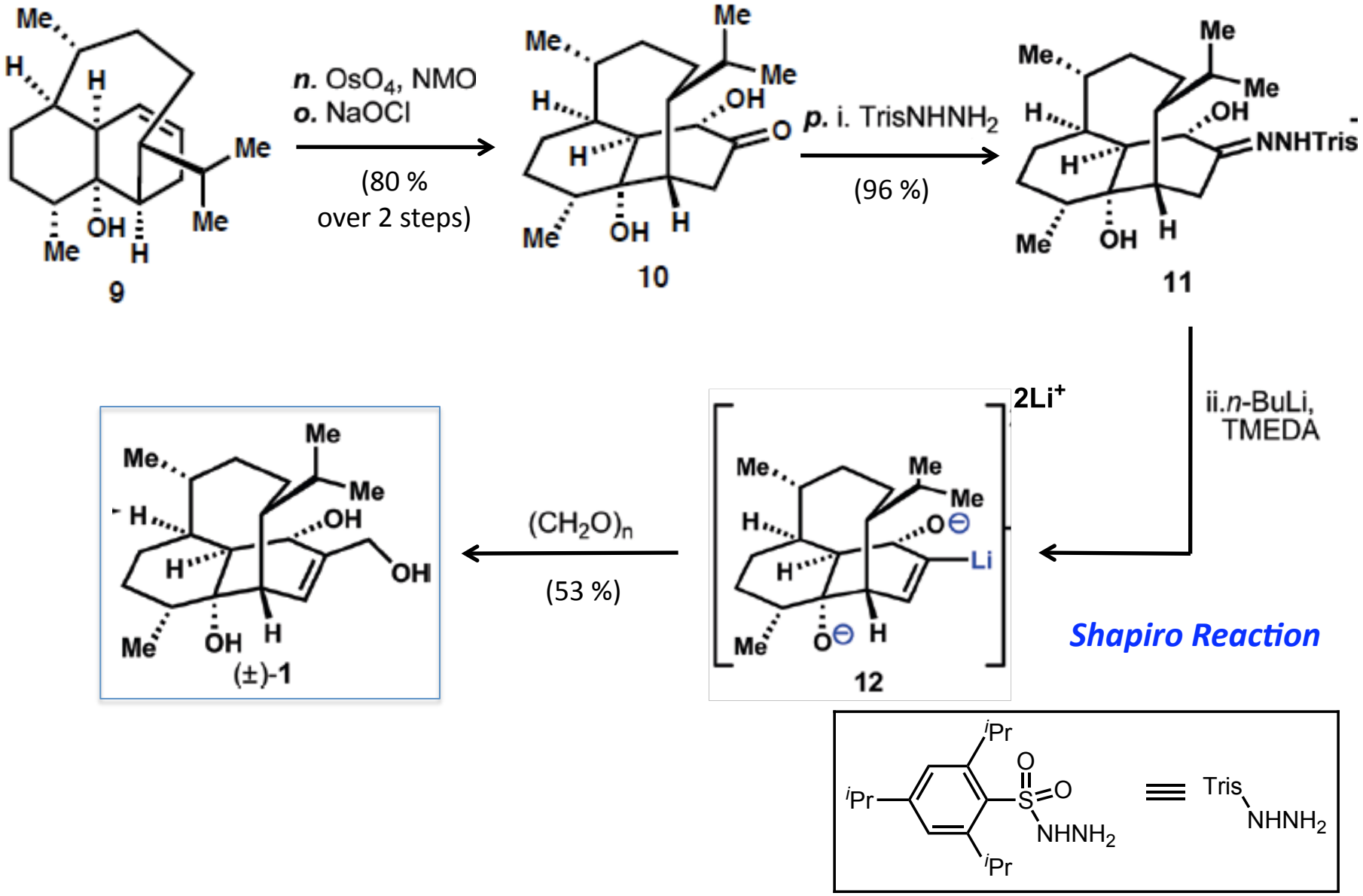
Synthesis of Fragment 9



A small sampling of "dead-end" intermediates



End-Game


Me
H
H
Me
OH
Me
Me
H
9
n. OsO4, NMO
o. NaOCl
(80 %
over 2 steps)
Me
Me
OH
O
H
Me
OH
H
10
p. i. TrisNHNH2
(96 %)
Me
Me
OH
NNHTris
H
Me
OH
H
11
ii.n-BuLi,
TMEDA
2Li+
Me
Me
Me
O⊖
H
Li
Me
O⊖
H
12
(CH2O)n
(53 %)
Me
Me
OH
H
OH
Me
OH
H
(±)-1
Shapiro Reaction
iPr
O
S
O
iPr
NHNH2
iPr
Tris
NHNH2

Conclusions

- A concise route to Vinigrol in 23 steps and 3 % overall yield from commercially available materials.
- First Synthesis of Vinigrol.
- Minimal use of protective group chemistry
- Nearly complete stereocontrol over all eight stereocentres
- Scalability of the route.
- Simple formation of the decahydro-1,5-butanonaphthalene ring system by way of inter and intramolecular Diels-Alder reactions followed by Grob fragmentation
- Highly selective functionalization of 2 by way of an unusual dipolar cycloaddition
- A Shapiro reaction that takes place via trianion

Things to do: An enantioselective variant of the first step.