A Concise Approach to Vinigrol

Thomas H. Maimone, Ana-Florina Voica and Phil S. Baran
The Scripps Research Institute, La Jolla, CA
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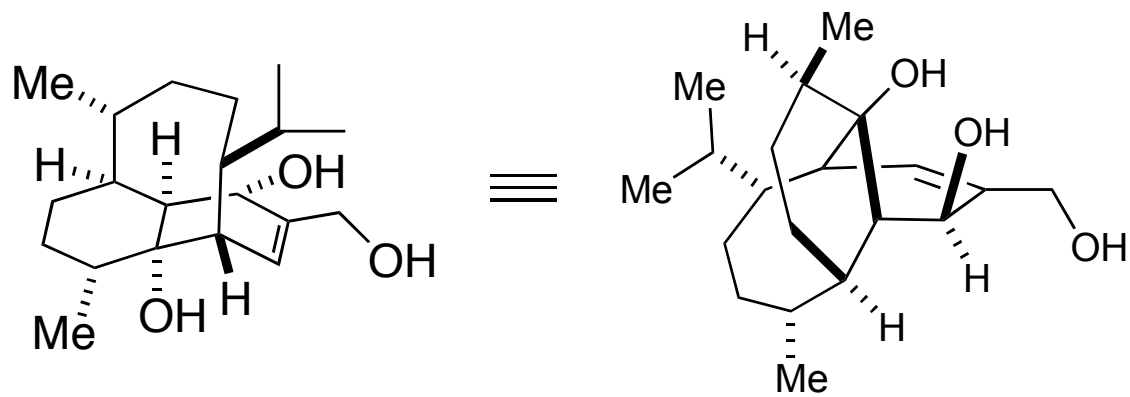
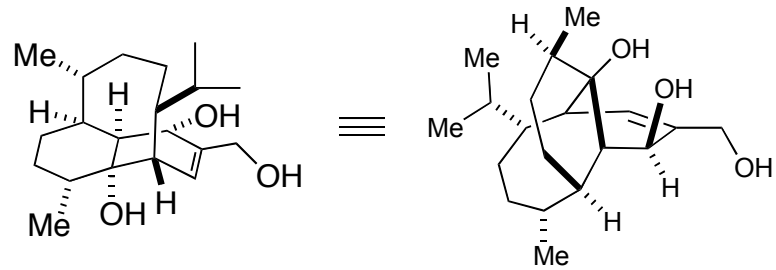


Current Literature Presentation
Wipf Research Group

Joshua Pierce - 3/29/08

Vinigrol: Isolation and Biological Activity



Vinigrol

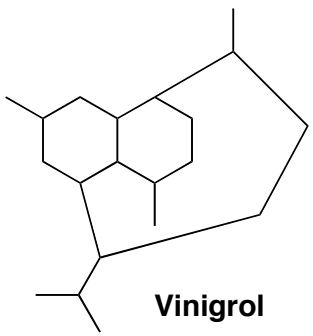
Isolated from the fungal strain *Virgaria nigra*

The structure and absolute configuration were determined using a combination of X-ray crystallography, ^{1}H NMR, and CD

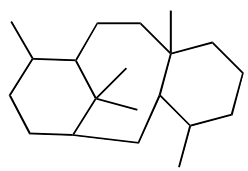
Shown to inhibit platelet activating factor (PAF)-induced platelet aggregation in human plasma with an IC_{50} of 33 nM; anti-hypertensive; TNF antagonist, along with many other activities.

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

The Chemical Challenge



Vinigrol
6-6-8



Taxane
6-8-6

17 publications
4 dissertations
0 total syntheses

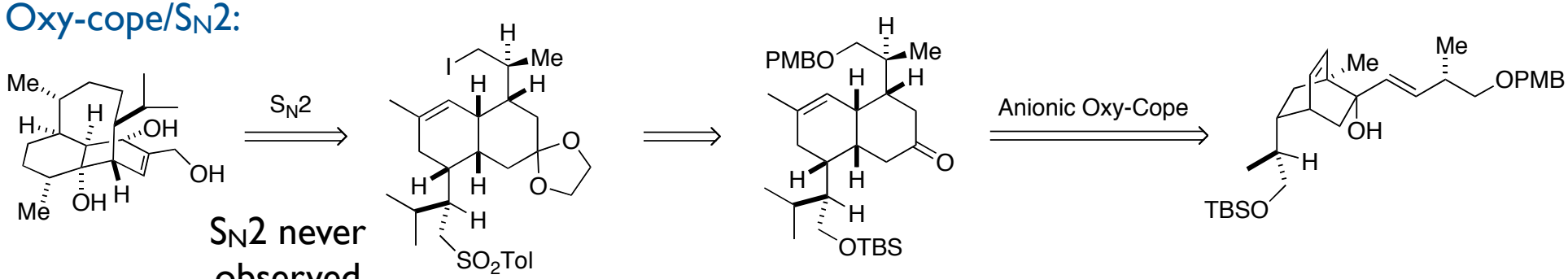
- 8 contiguous stereocenters

- multiple sites of oxygenation

For a review of terpene synthesis, see: Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007**, *3*, 396.

Synthetic Approaches: Paquette

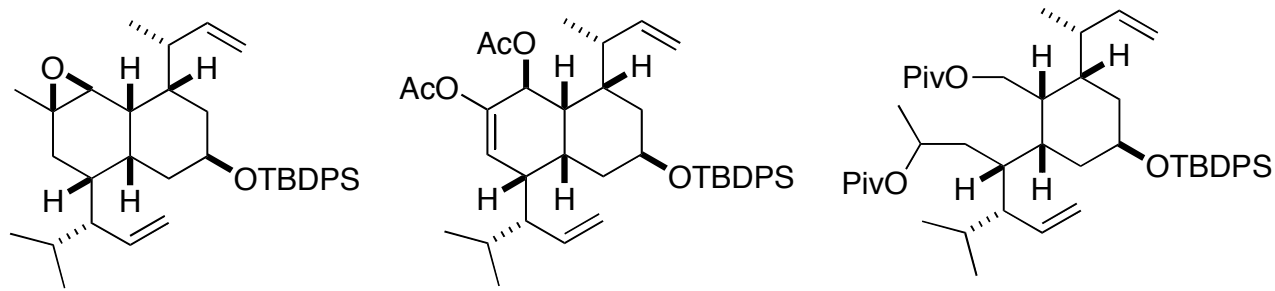
Oxy-cope/S_N2:



S_N2 never observed

L. A. Paquette, R. Guevel, S. Sakamoto, I. H. Kim, J. Crawford, *J. Org. Chem*. **2003**, *68*, 6096.

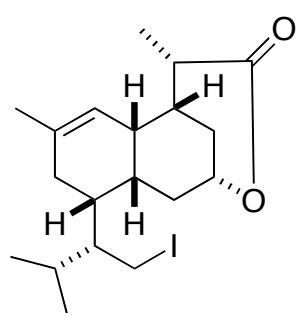
Ring-Closing Metathesis:



Metathesis not observed in any cases

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

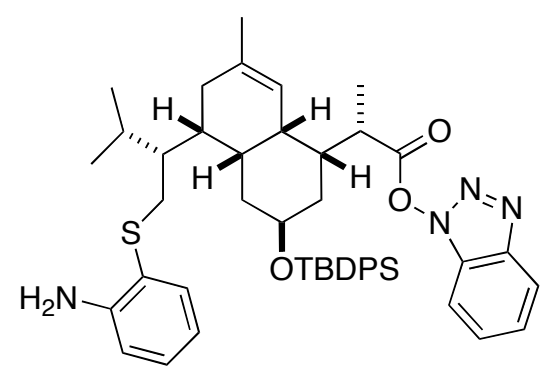
Lactone Bridge:



Never able to close ring in either case.

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

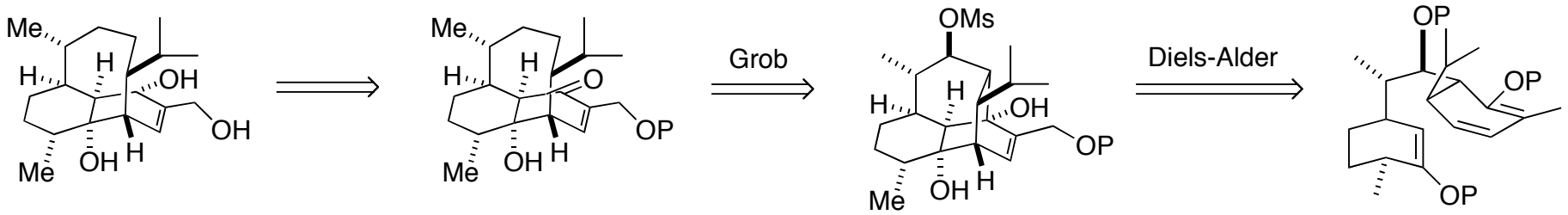
Ring-Contraction:



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

Synthetic Approaches: Corey

Initial Retro:

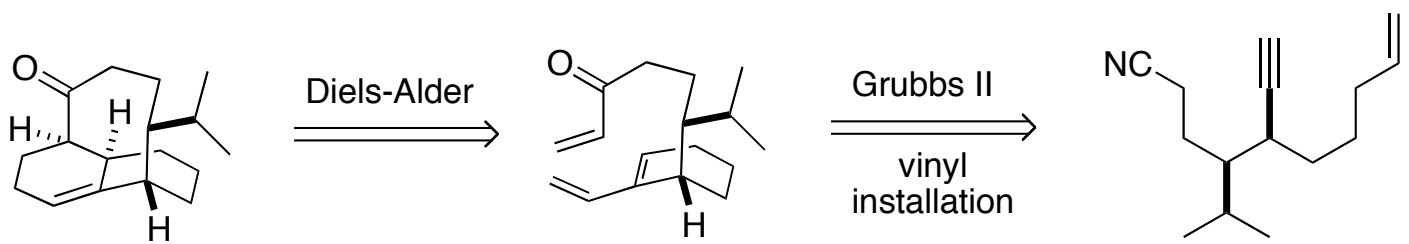


Grob fragmentation proposed as method to generate difficult 8-membered ring; never attempted in Corey lab.

Diels-Alder never successful; attempted many variations (inverse electron demand, intermolecular, etc.)

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

Synthetic Approaches: Barriault



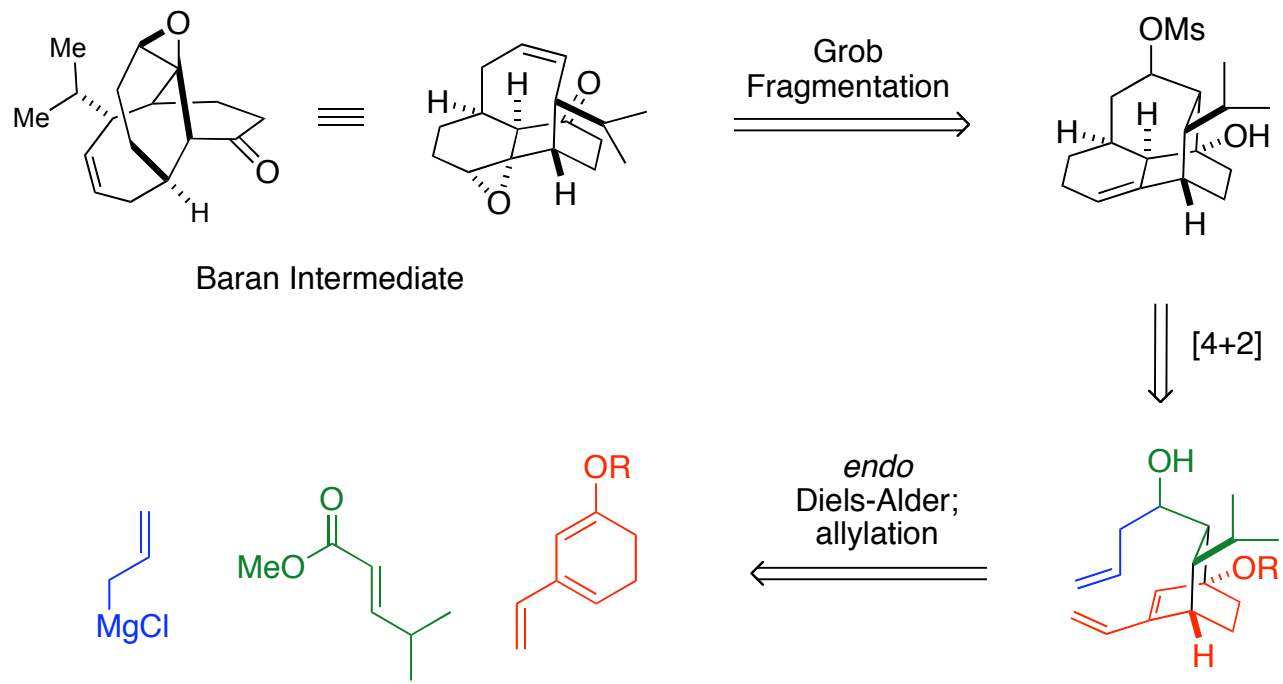
Diels-Alder proceeds in 99% yield at -78 ˚C using $BF_3 \cdot OEt_2$

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

For another IMDA approach, see: M. S. Souweha, G. D. Enright, A. G. Fallis *Org. Lett.* **2007**, *9*, 5163.

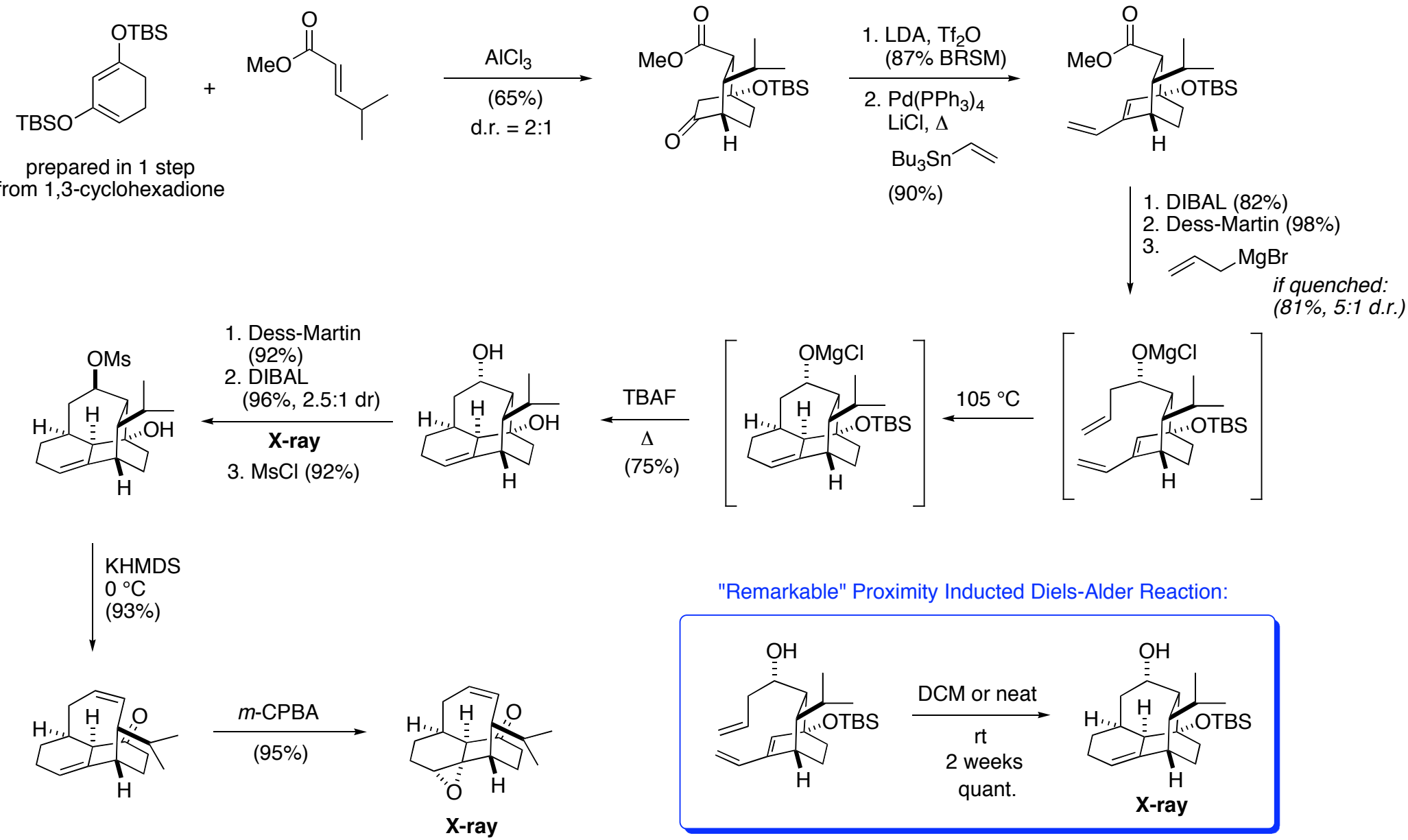
For additional approaches not mentioned here, see ref #3 of title paper

Retrosynthetic Analysis of Carbon Skeleton:



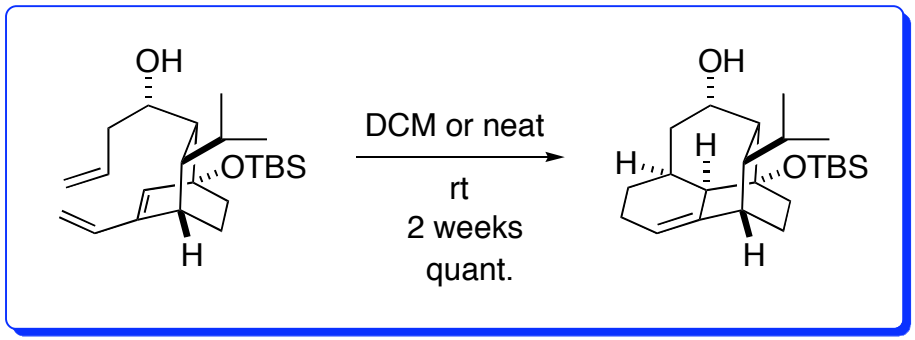
"Herein we posit a logical blueprint and the necessary empirical validation for an exceptionally concise total synthesis of 1 (vinigrol)."

Baran's Synthesis of Vinigrol Core



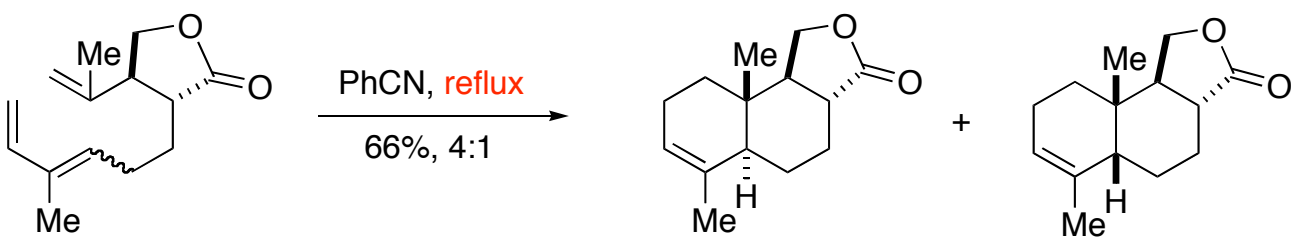
A Closer Look: Intramolecular Diels-Alder Reactions

"Remarkable" Proximity Inducted Diels-Alder Reaction:



"To the best of our knowledge, this is the only example of a completely electron-neutral diene and simple olefin taking part in a non-catalyzed cycloaddition at ambient temperature"

Literature shows examples of electron neutral alkenes in DA, but always at elevated temperatures

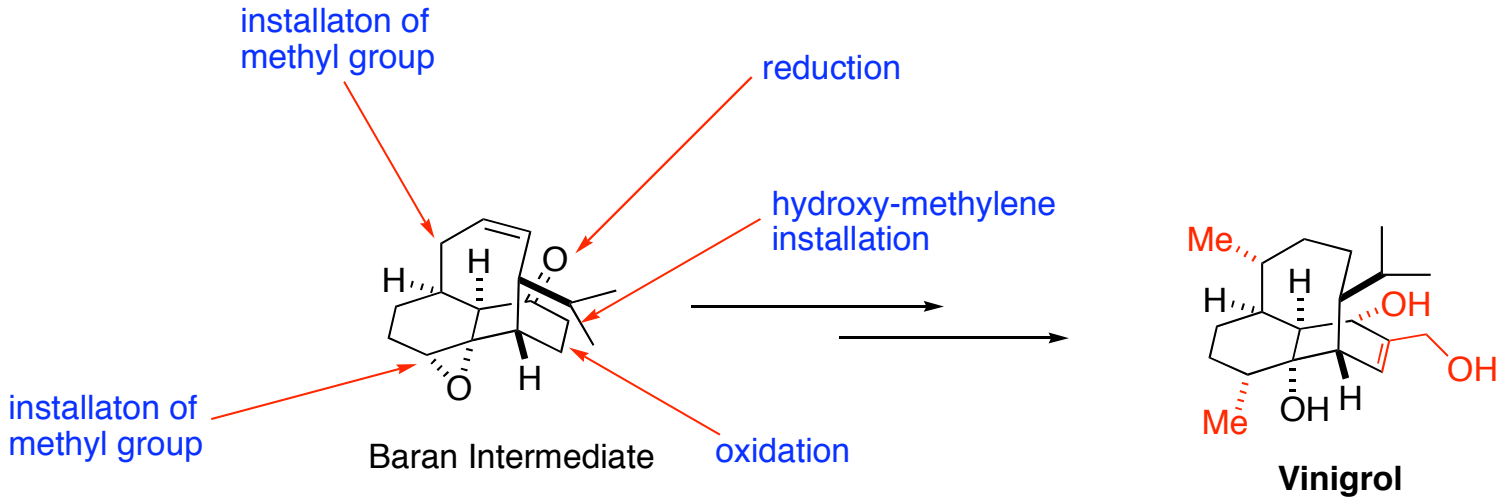


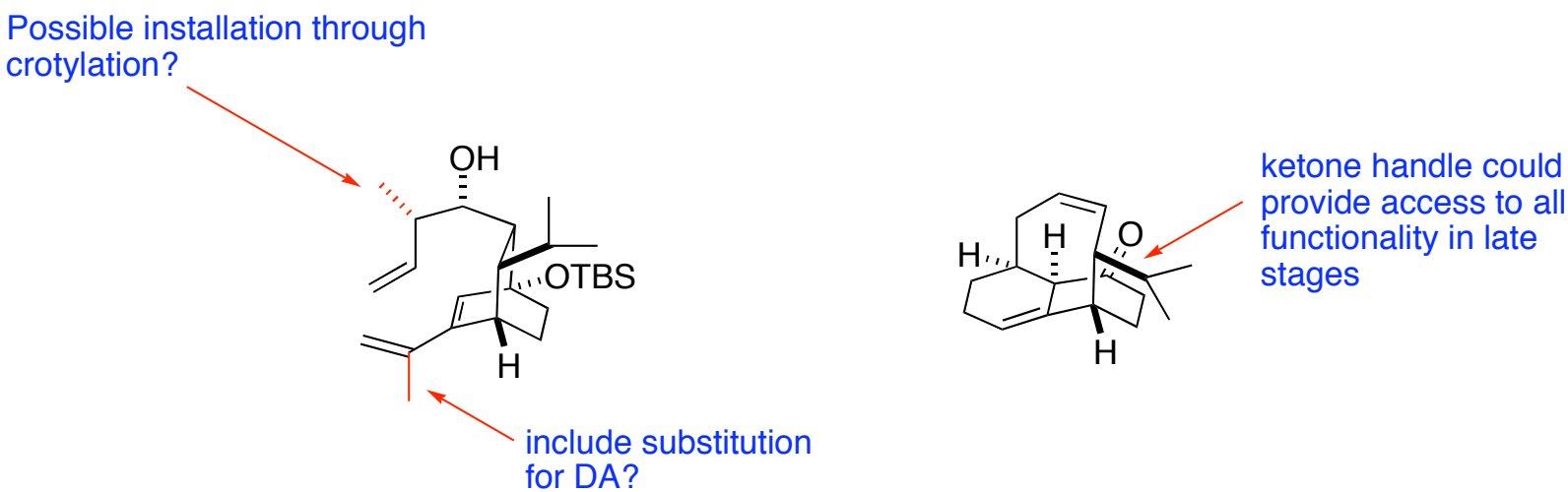
Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**. *100*, 6289.
Taber, D. F.; Nakajima, K.; Xu, M.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 4501.

Most examples involve activated alkenes and often involve catalysis.

For reviews of IMDA, see: (a) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem* **2002**,*114*, 1742. (b) K. Takao, R. Munakata, K. Tadano, *Chem. Rev.* **2005**, *105*, 4779.

What Lies Ahead...





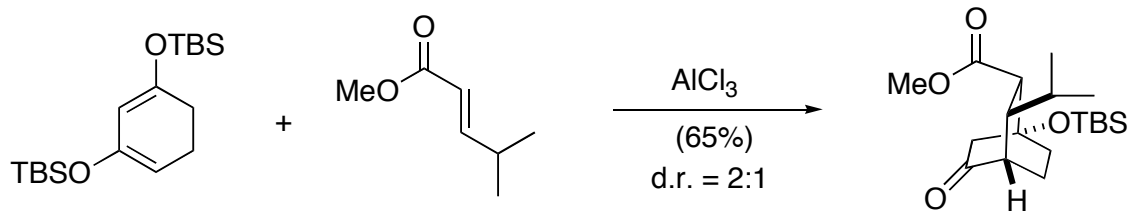
First total synthesis of vinigrol seems within reach - Publication of core "un-Baran like"

Protecting Group Free Synthesis

What Constitutes a Protecting Group?

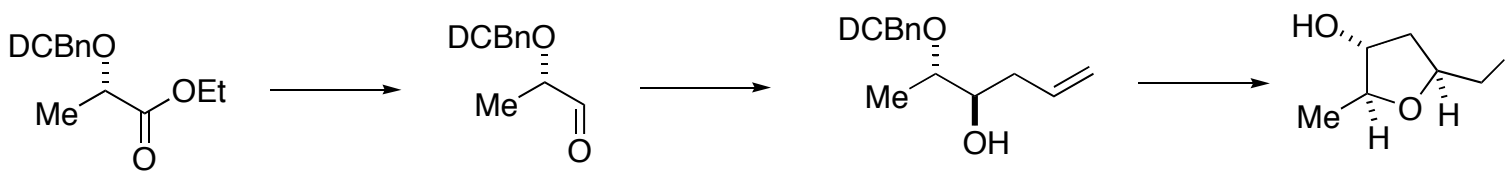
Reference 9 (title paper):

"As the silyl groups are necessary to maintain the diene form of 8, they are not considered to be a protecting group."

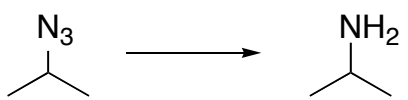


It's all about intent...

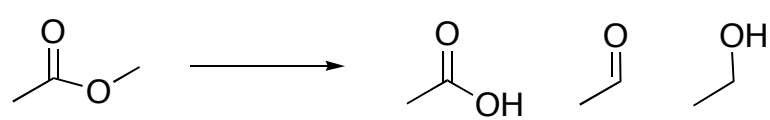
"And uses a dichlorobenzyl moiety not as a protecting group, but as a group that controls the stereochemistry of the ring-forming iodo-etherification reaction"



Where is the line between functional group interconversion and protecting group usage?



If carried through more than one step, is azide a PG?



Oxidation state adjustment vs PG?

It is clear that minimization (or elimination) of protecting groups is providing access to novel chemistry and allowing for rapid access to complex targets; however, the use of "protecting group free" is up for debate in some cases.

For interesting discussion, see:

P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404.
R.W. Hoffmann, *Synthesis* **2006**, 3531.

Conclusions

A rapid synthesis of the vinigrol core has been developed (11 steps, ~20% yield)

Synthesis has been realized though combination of careful planning with insight from previous synthetic successes, failures and proposals.

Further work to elaborate the carbon framework to vinigrol should provide the first synthesis of this historical terpene target.

Or, as Professor Baran would put it:

"The concise, high-yielding (ca. 20%yield from 8) route to 5 attests to the strength of the underlying logic of this synthesis plan ... Approximately half of the steps in this approach either make C C bonds or strategically break them. Careful sequence choreography and redox accounting in this nine-step sequence has led to a minimization of protecting group chemistry. Efforts to streamline this sequence further and apply it to a total synthesis of 1 are well underway."