Scalable Total Synthesis of (-)-Vinigrol

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Checker: Yang Zhao
Date: 2019/04/01

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J. Am. Chem. Soc. **2019**, *141*, 3440.

Contents

CV of Prof. Tuoping Luo

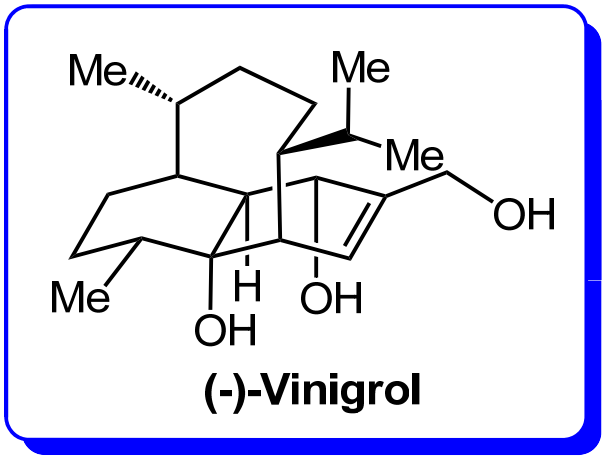
Background:

- **2001-2005** B.S., Peking University
- **2005-2011** Ph.D., Harvard University
- **2011-2013** Postdoc, H3 Biomedicine Inc.
- **2013-Now** Principal Investigator, Peking University
  Provisional Principal Investigator,
  Peking University-Tsinghua University

Research Interests:

- ✓ Exploring and applying novel chemical reactions with the goal to advance synthetic organic chemistry and chemical biology
- ✓ Discovering innovative approaches to address the demanding medical needs of human beings

Introduction

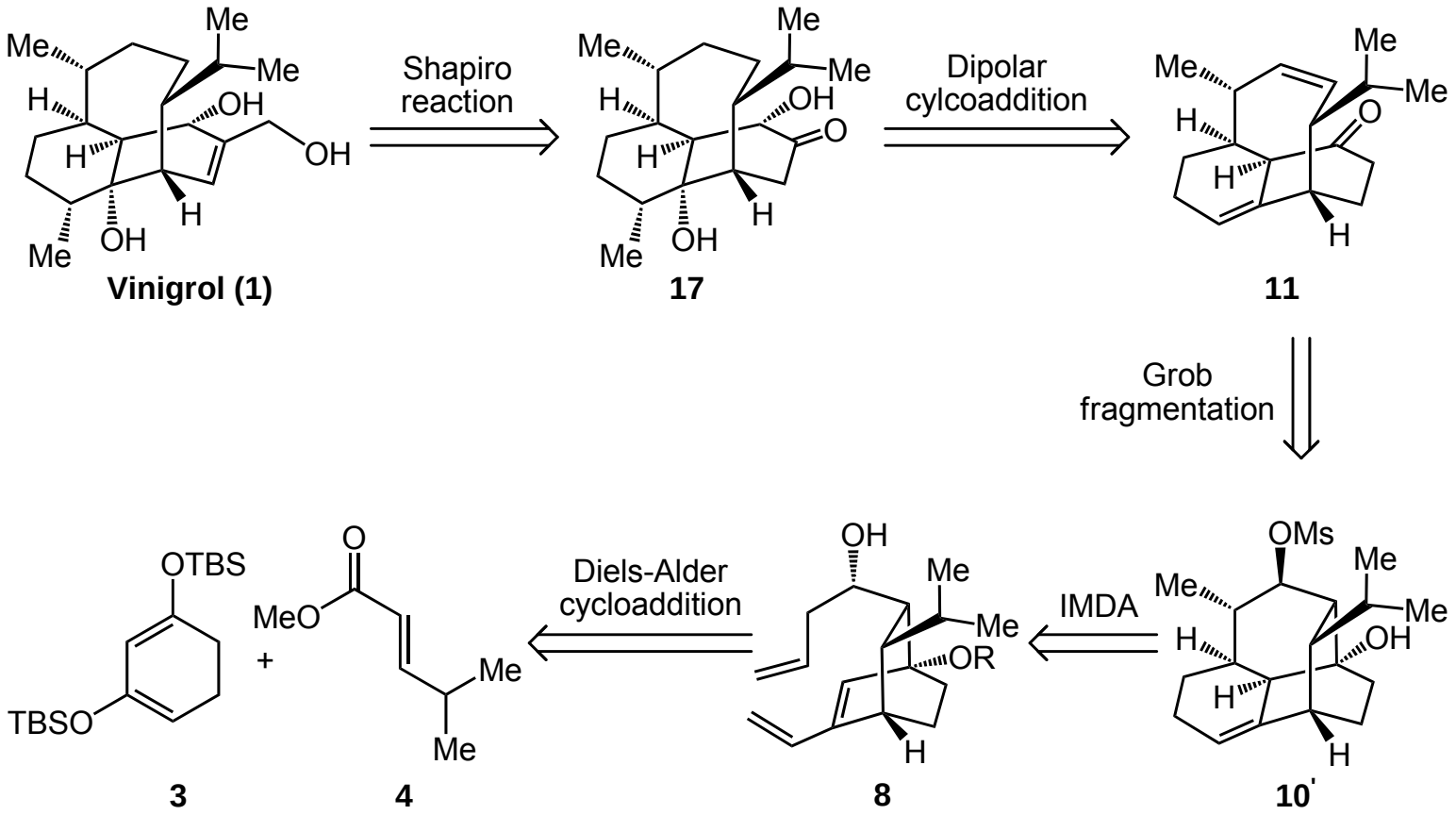


(-)-Vinigrol

- Isolated from a fungal strain *Virgaria nigra* F-5408 in 1987;
- Exhibiting potent antihypertensive and platelet aggregation-inhibiting properties; an antagonist for tumor necrosis factor α;
- The 6-6-8 tricyclic ring system with the axial four-carbon tether bridging the densely decorated *cis*-decalin core. Eight contiguous stereogenic centers.

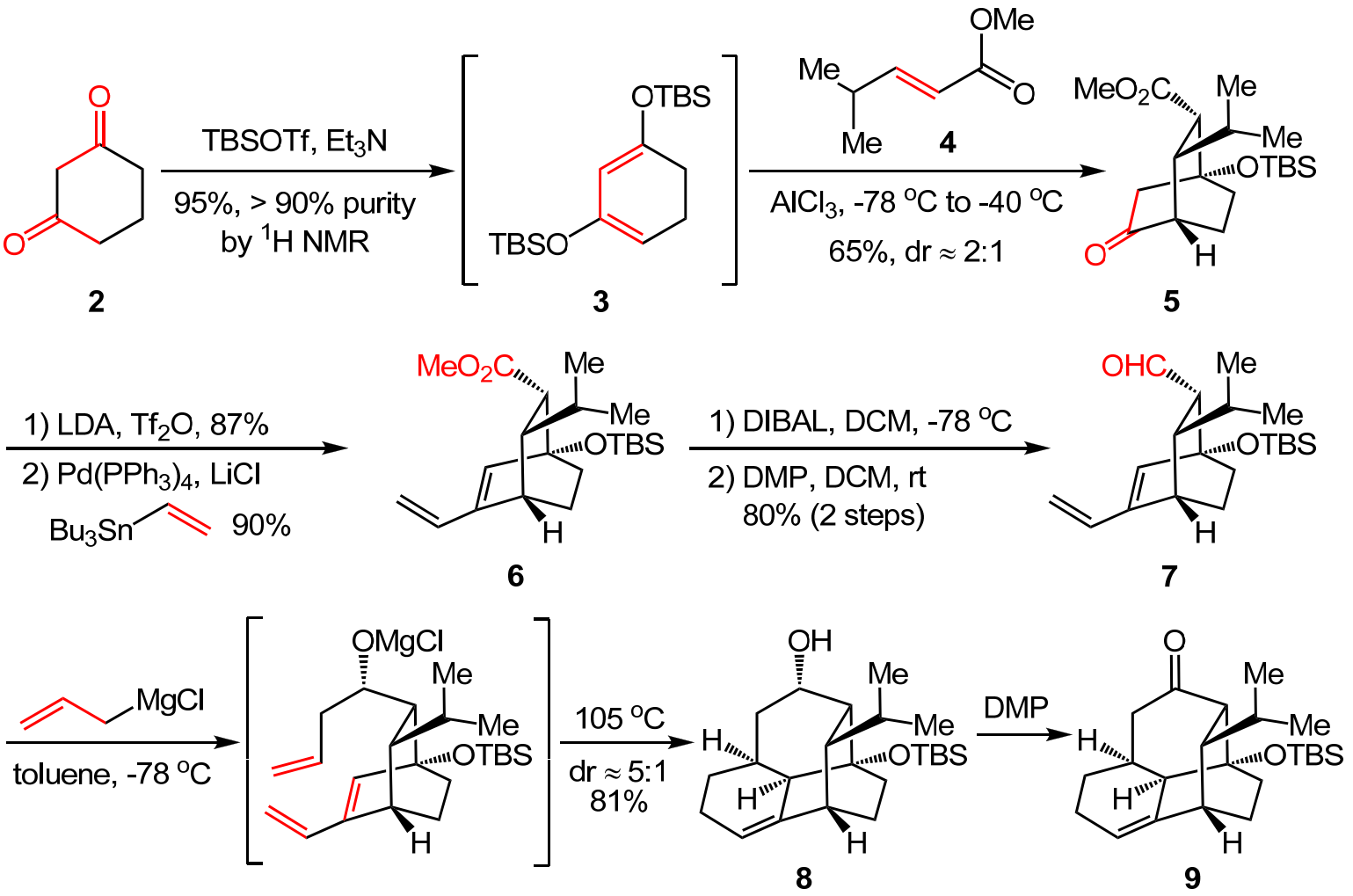
Hashimoto, T. *et al. J. Org. Chem.* **1987**, *52,* 5292.

Retrosynthetic Analysis



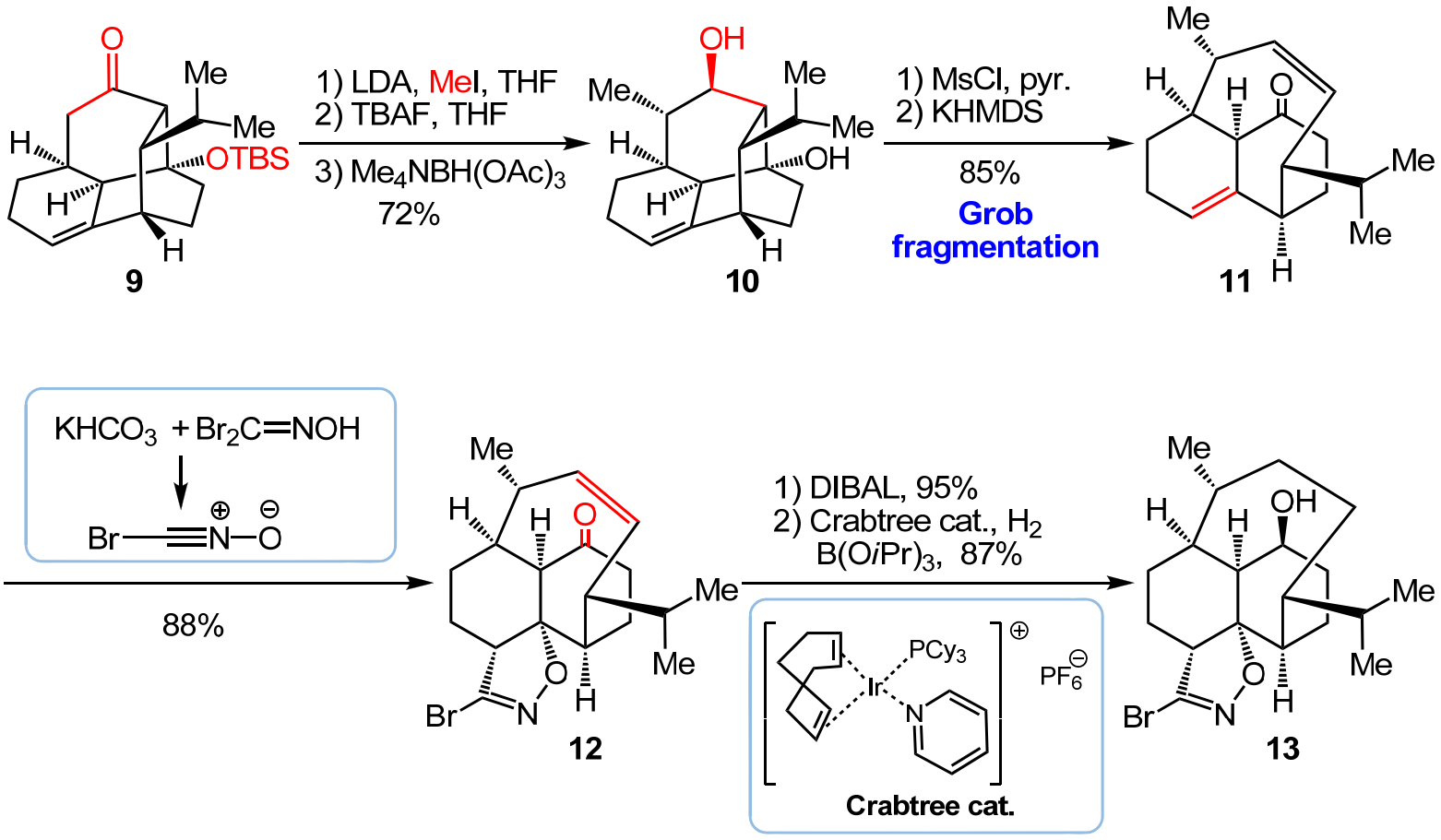
Baran, P. S. *et al. J. Am. Chem. Soc.* **2009**, *131*, 17066.

Synthesis of Compound 9

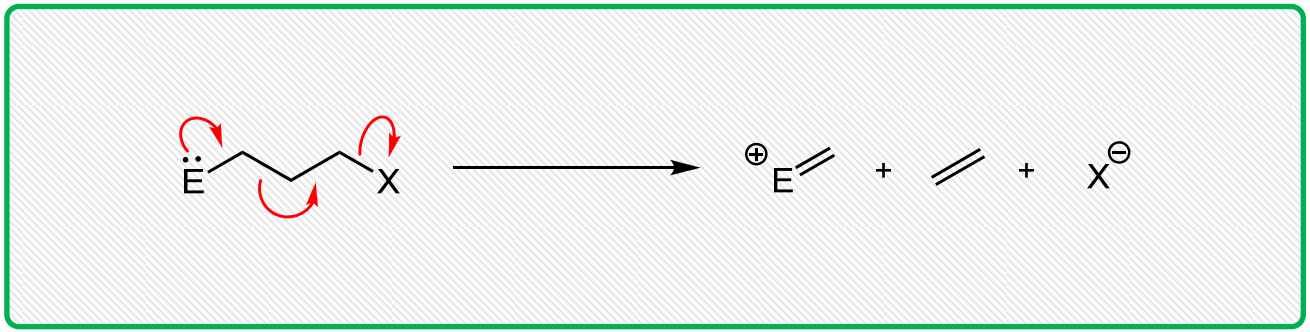


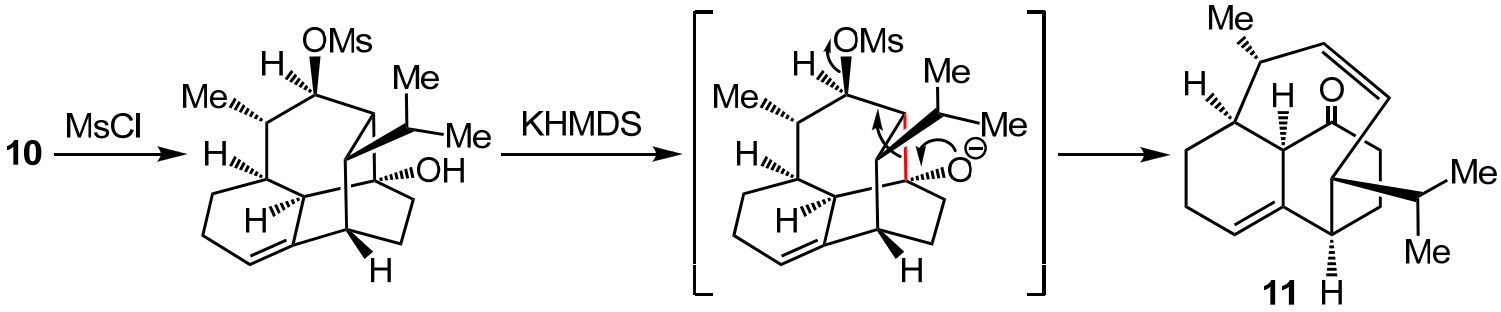
Baran, P. S. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 3054.

Synthesis of Compound 13

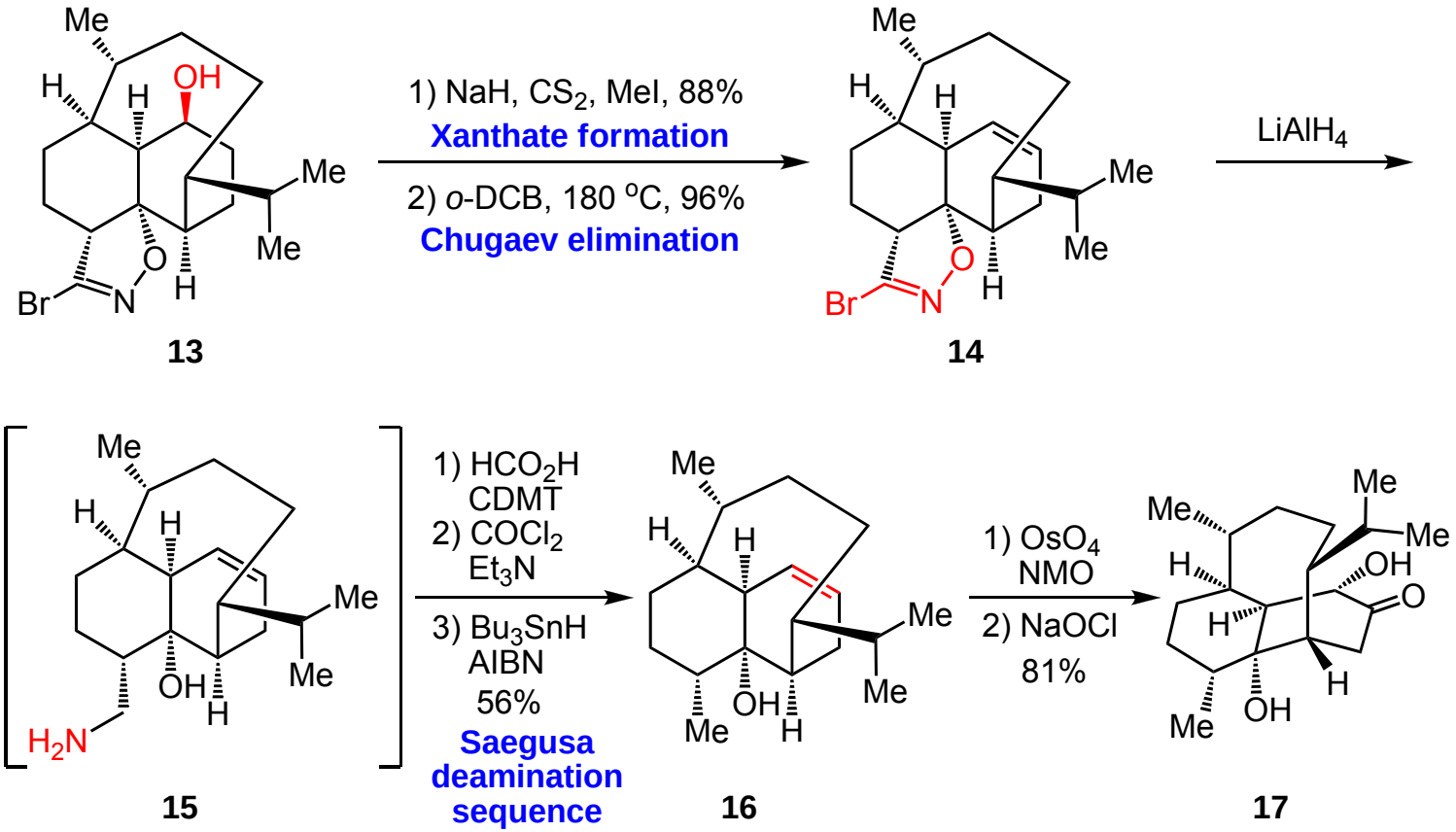


Grob Fragmentation

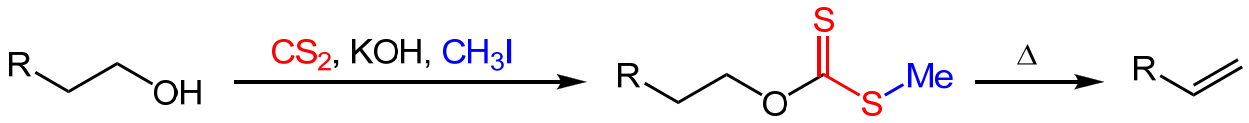




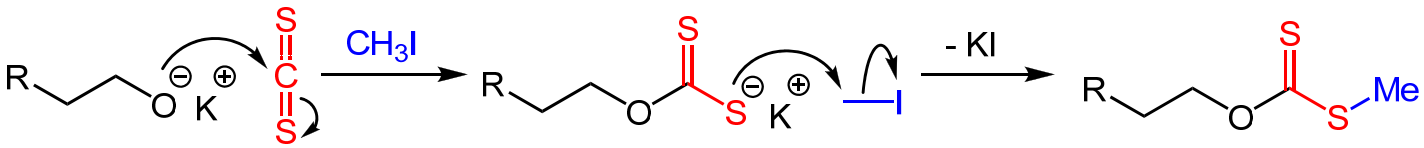
Synthesis of Compound 17



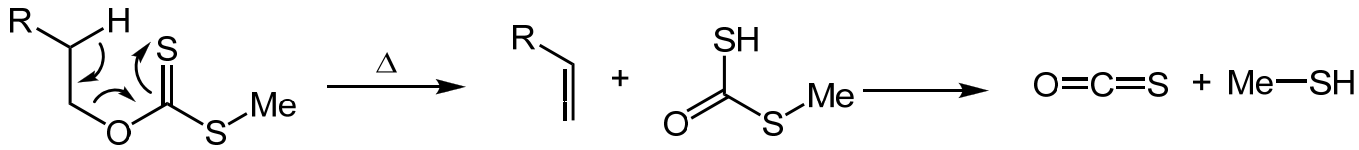
Xanthate Formation and Chugaev Elimination



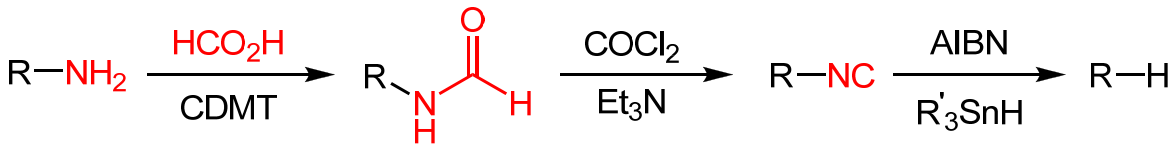
Xanthate Formation



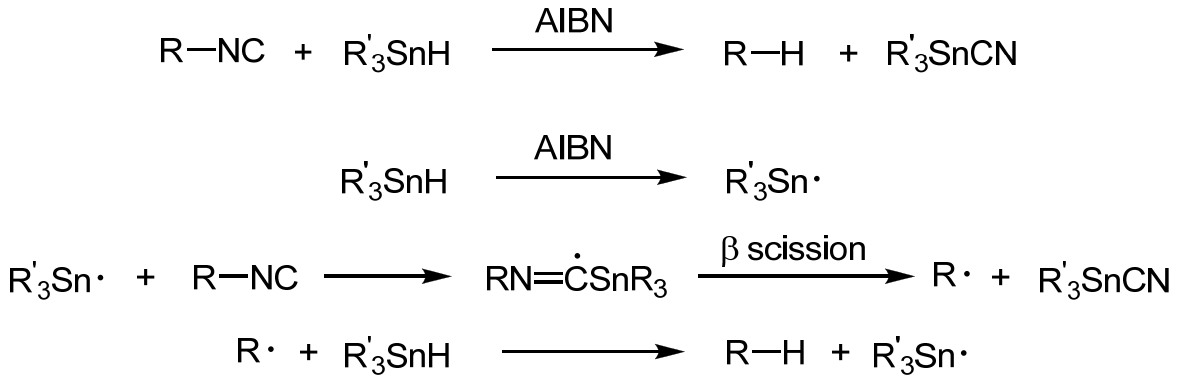
Chugaev Elimination



Saegusa Deamination Squence

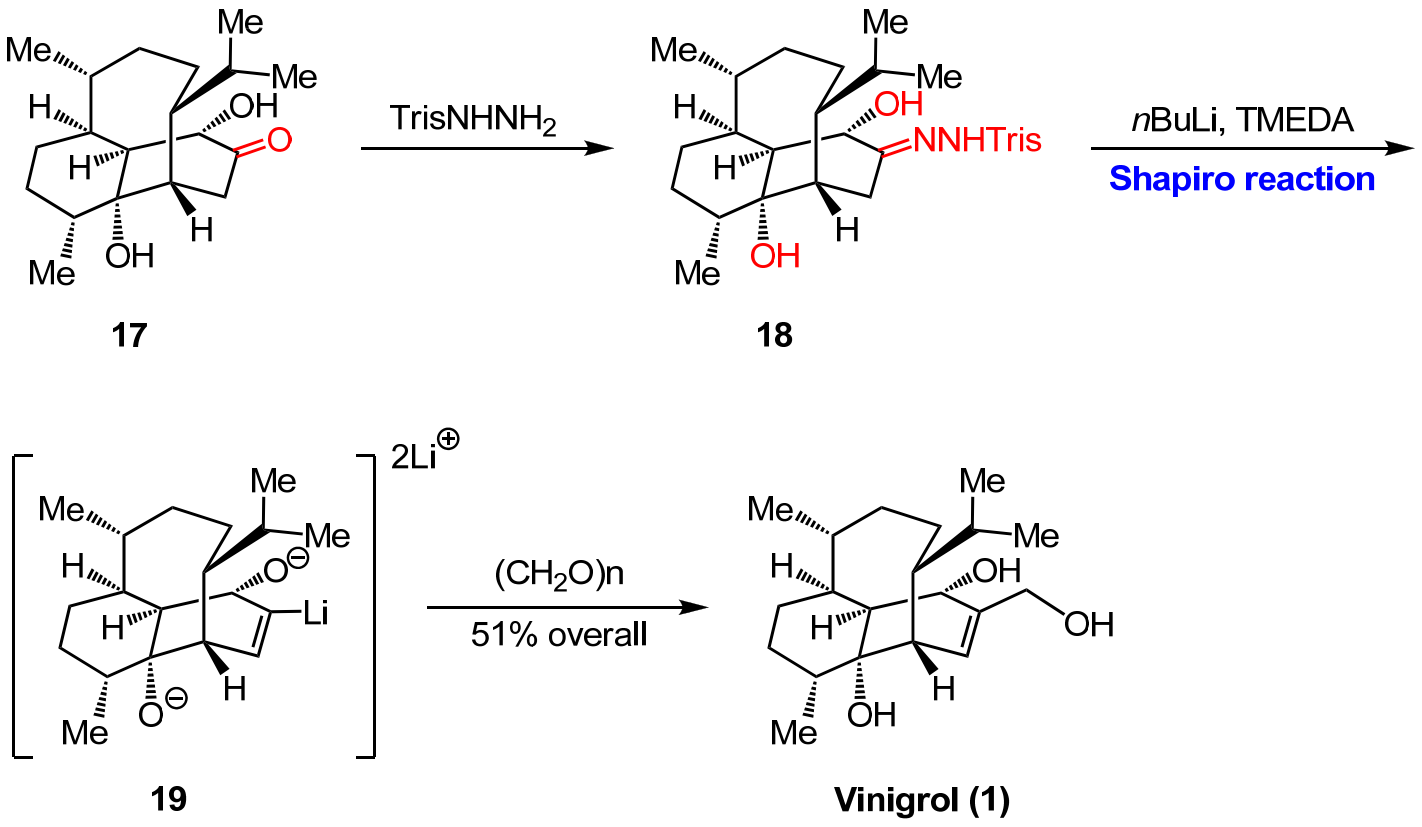


Radical Reaction of Isocyanide with Organotin Hydride

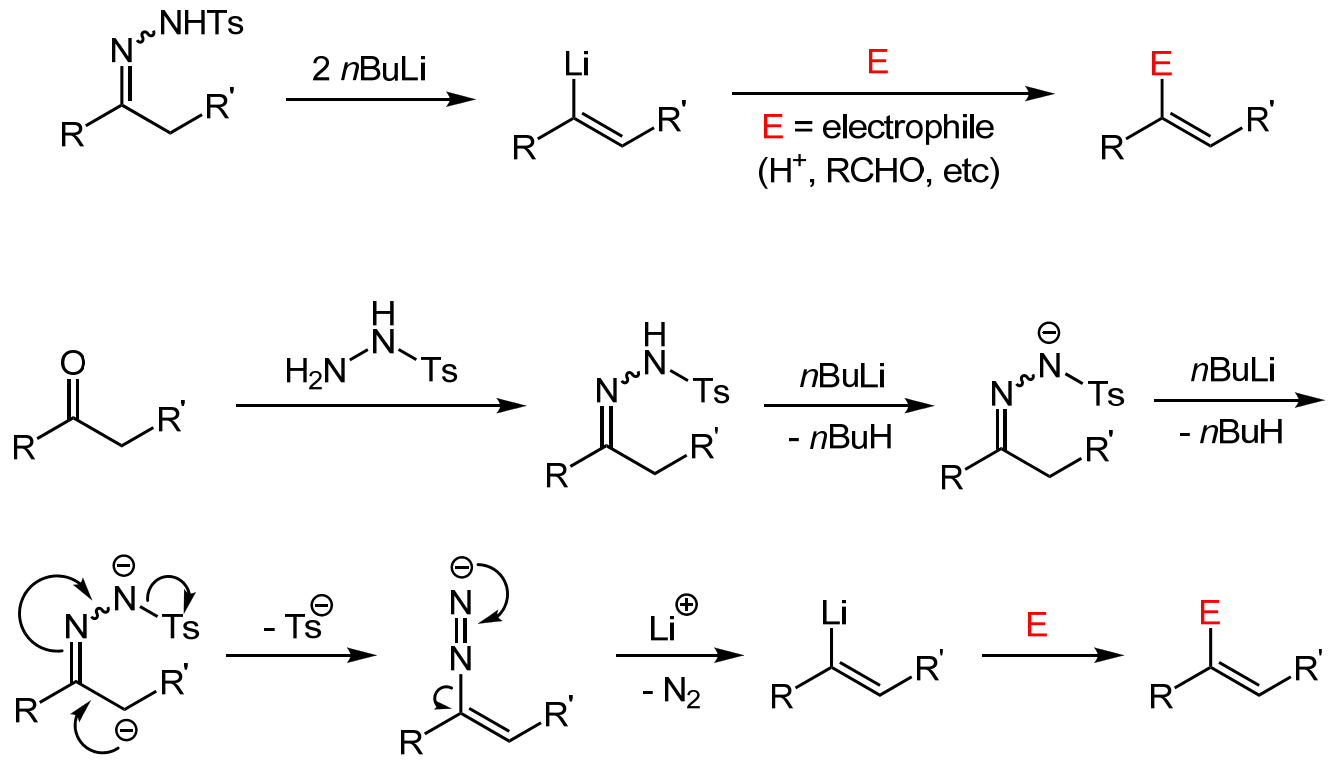


Saegusa, T. *et al. J. Am. Chem. Soc.* **1968**, *90*, 4182.

Synthesis of Vinigrol

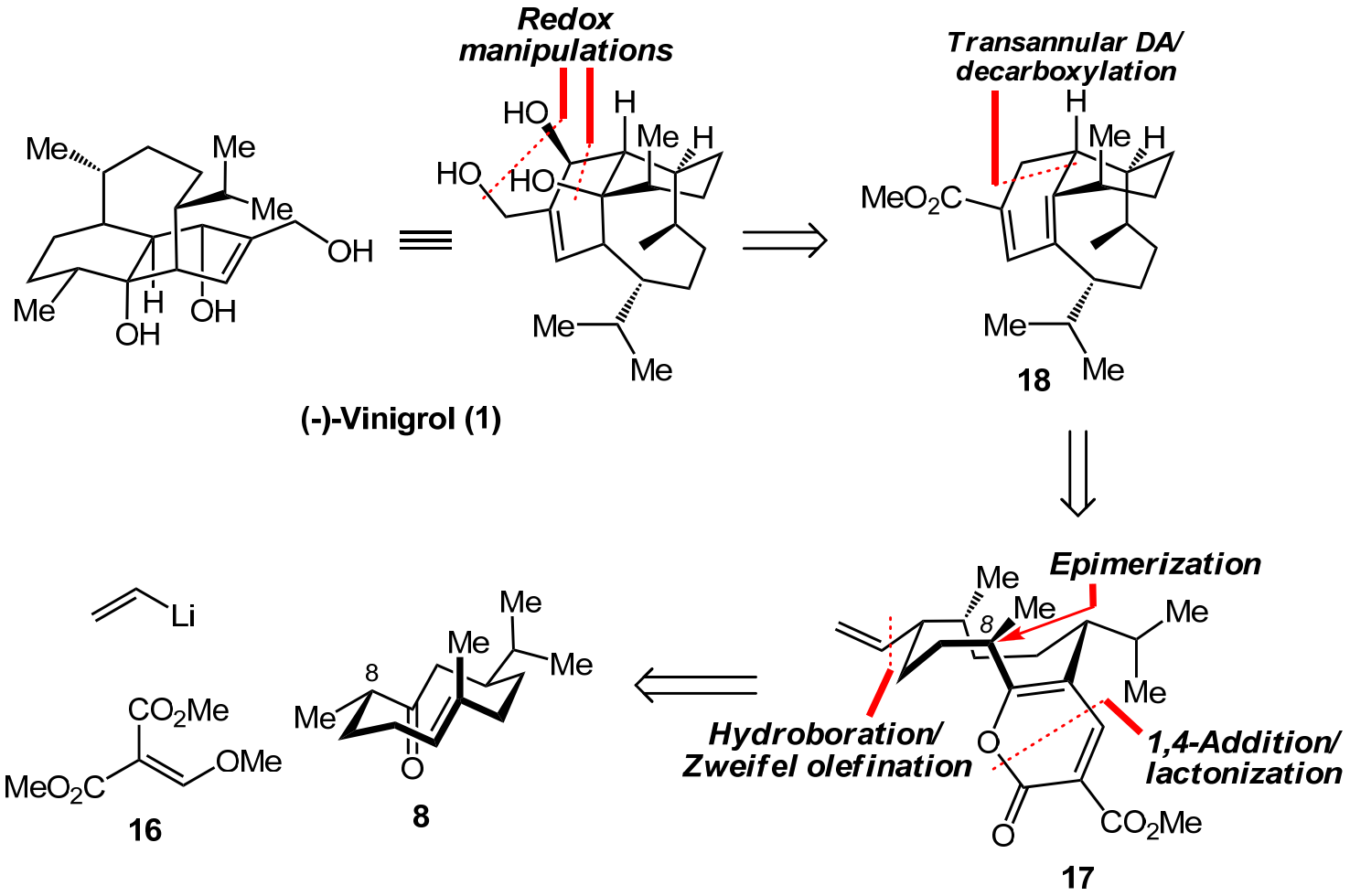


Shapiro Reaction



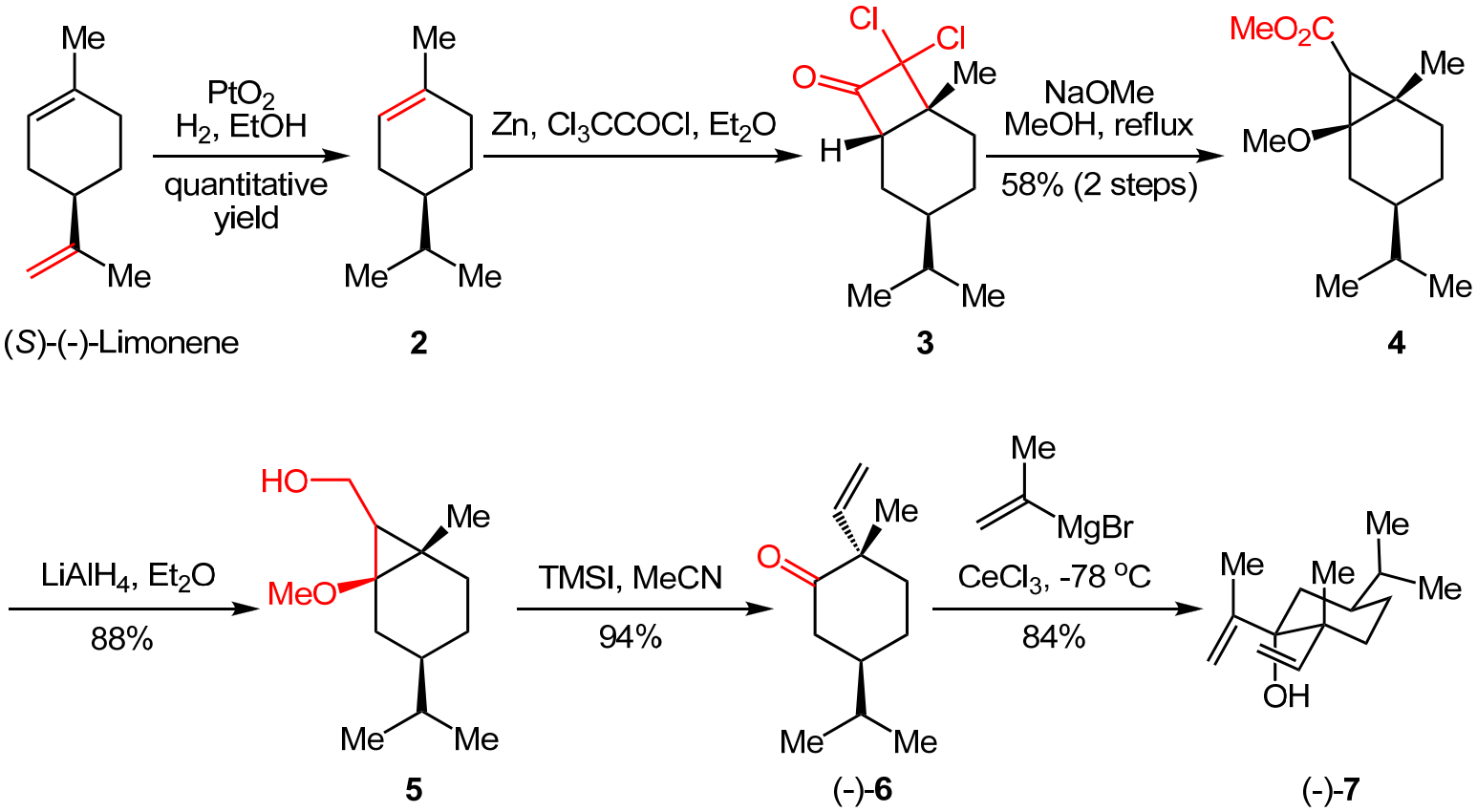
Shapiro, R. H. *et al. J. Am. Chem. Soc.* **1967**, *89*, 5734.

Retrosynthetic Analysis



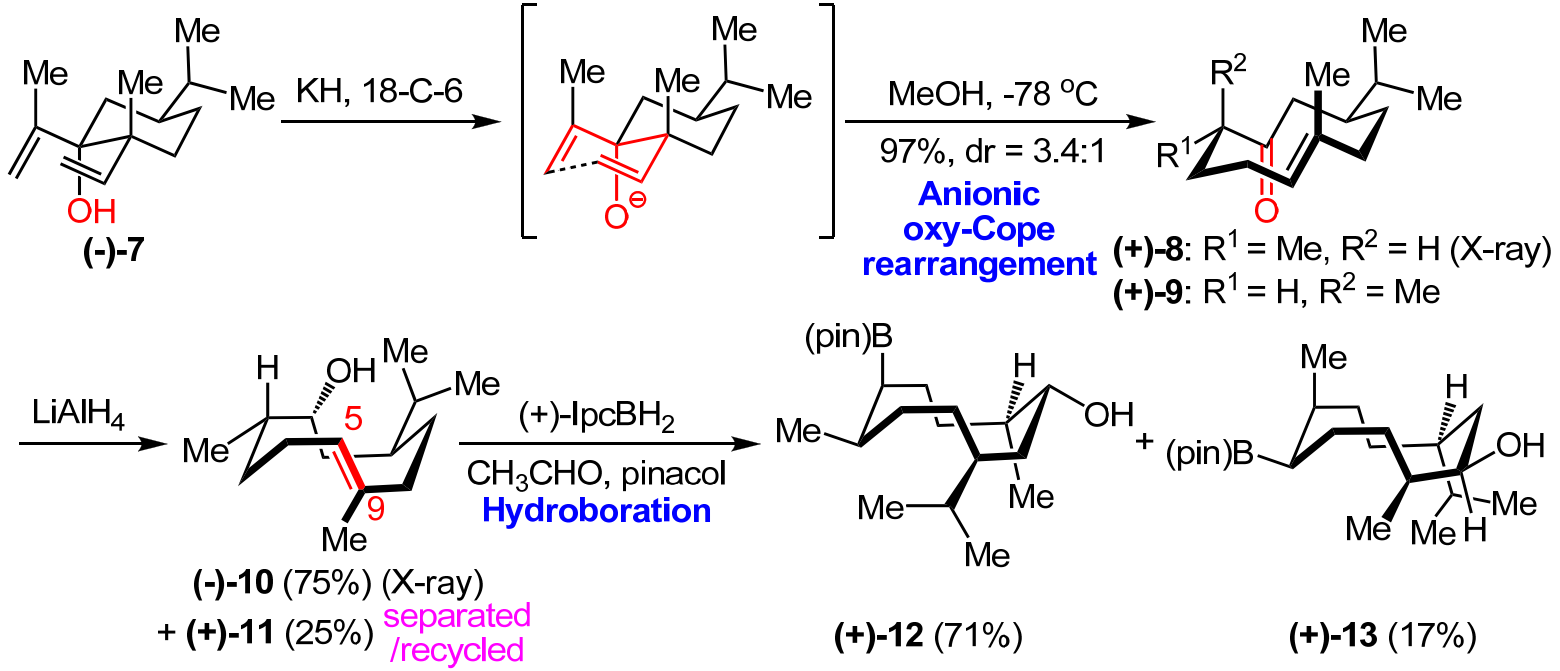
Luo, T. *et al. J. Am. Chem. Soc.* **2019**, *141*, 3440.

Synthesis of Compound (-)-7

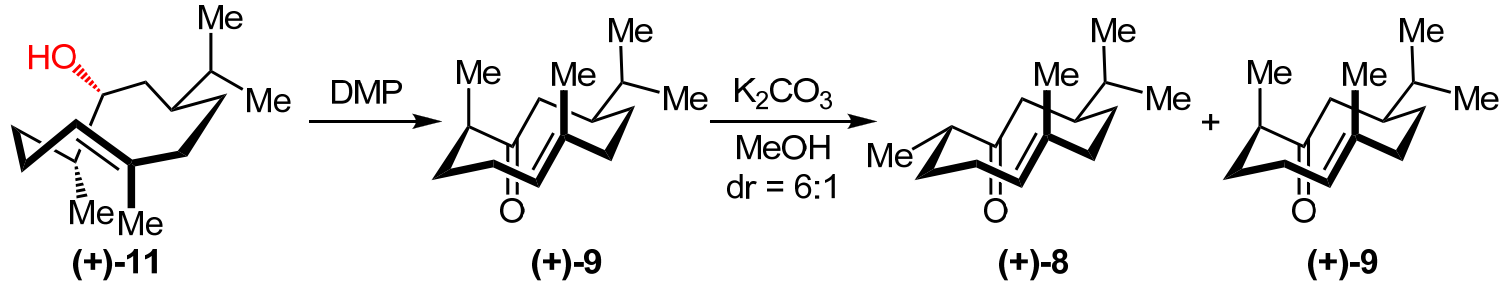


Mehta, G. et al. *Indian J. Chem. Sect B* **1998**, *37B*, 201.

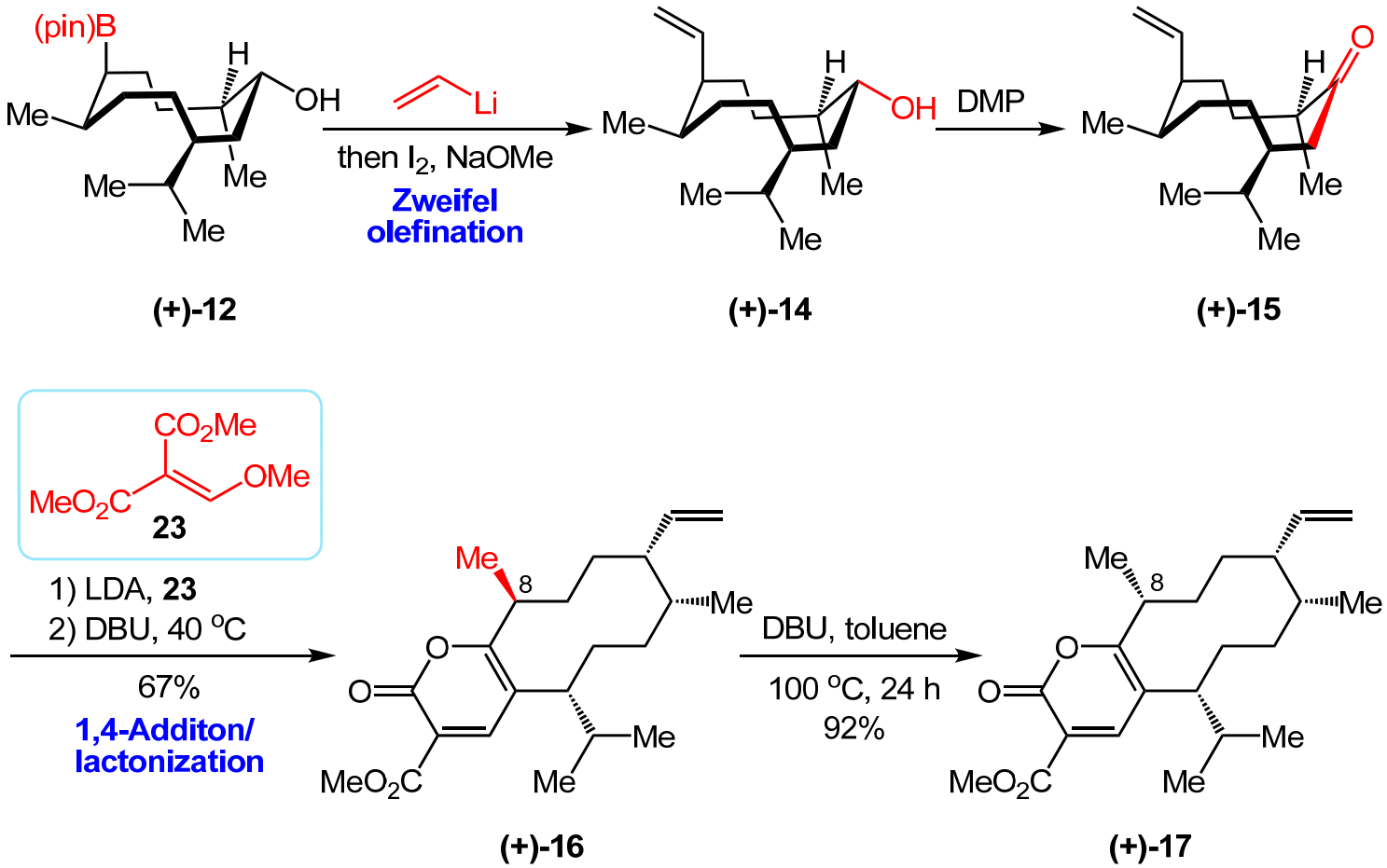
Synthesis of Compound (+)-12



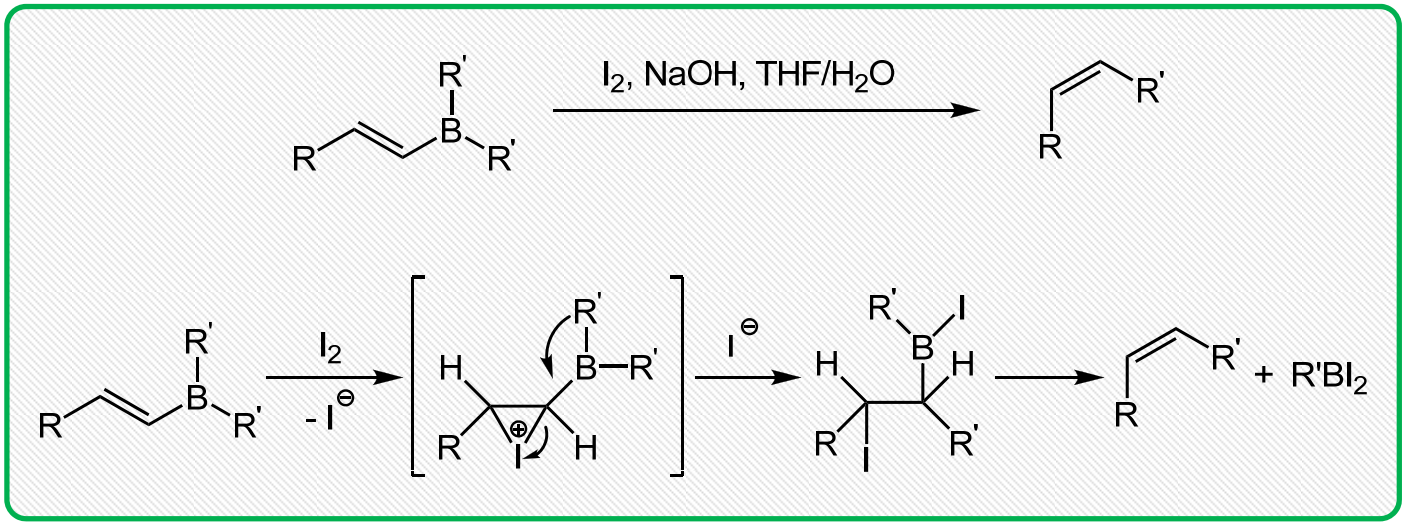
The Recyle of Compound (+)-11 to Compound (+)-8



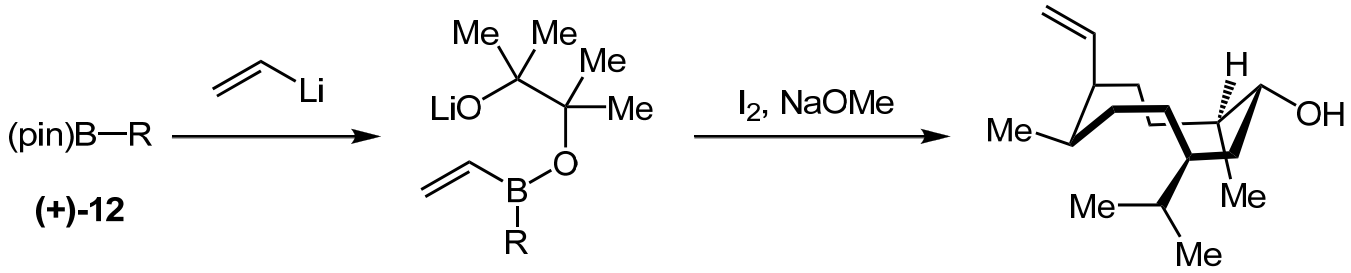
Synthesis of Compound (+)-17



Zweifel Olefination



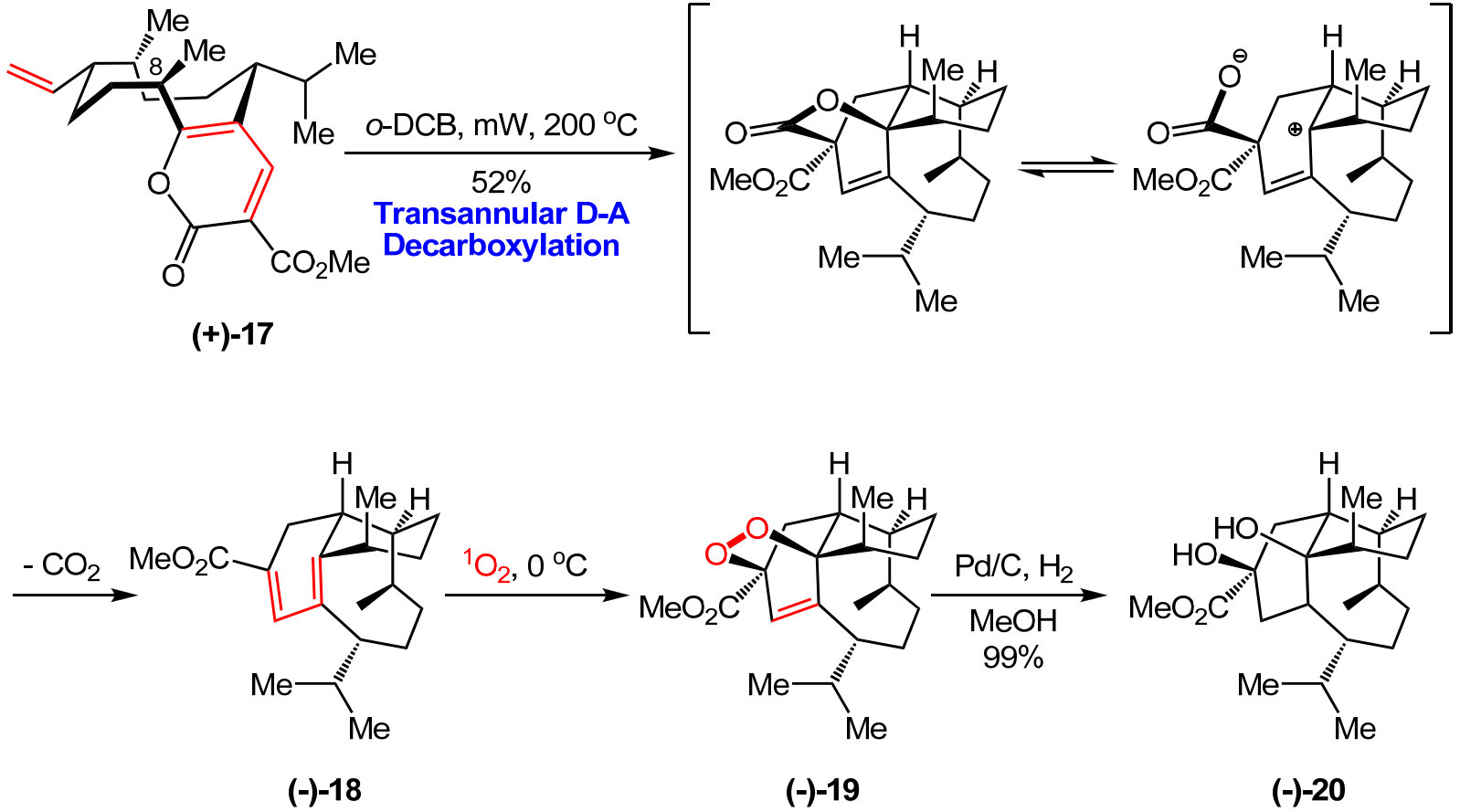
Zweifel, G. et al. *J. Am. Chem. Soc.* **1967**, *89*, 3652.



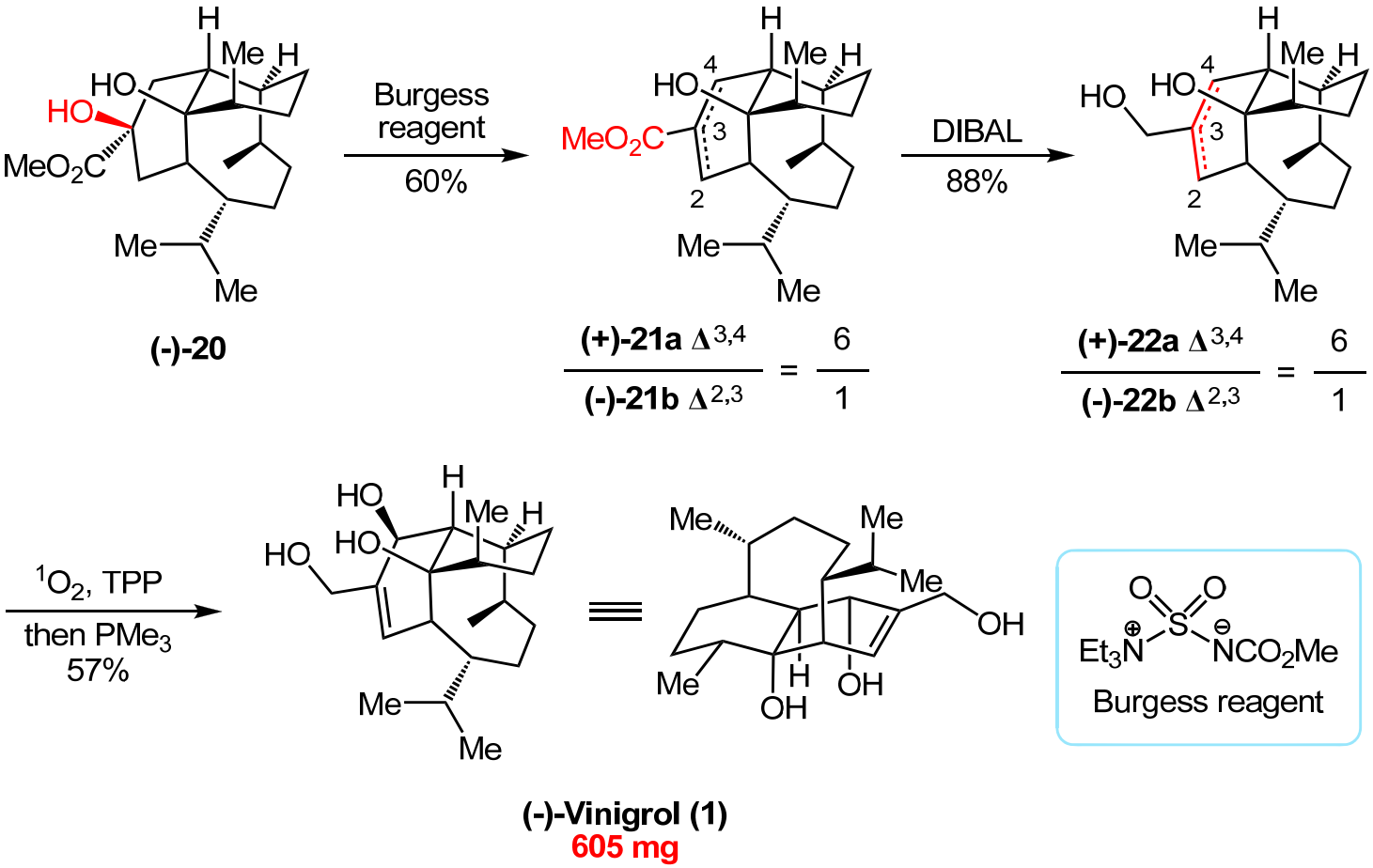
(+)-12

(+)-14

Synthesis of Compound (-)-20

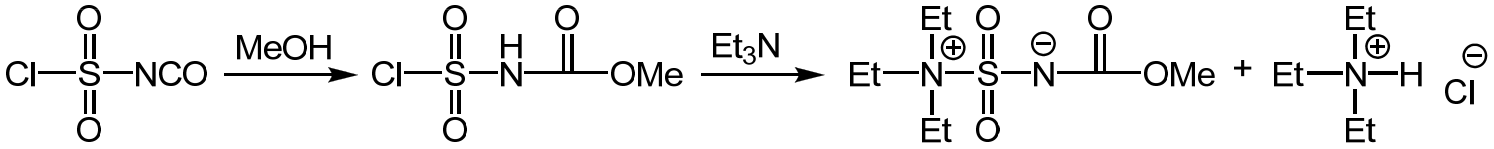


Synthesis of (-)-Vinigrol

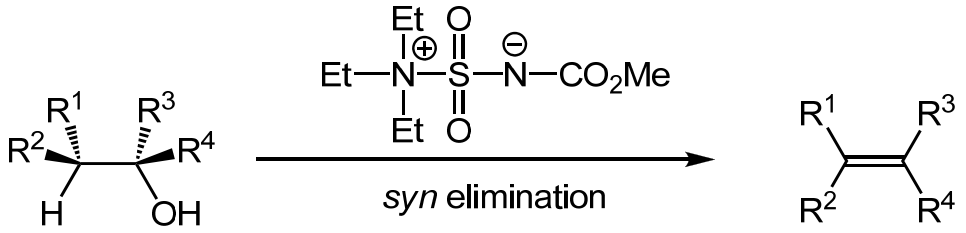


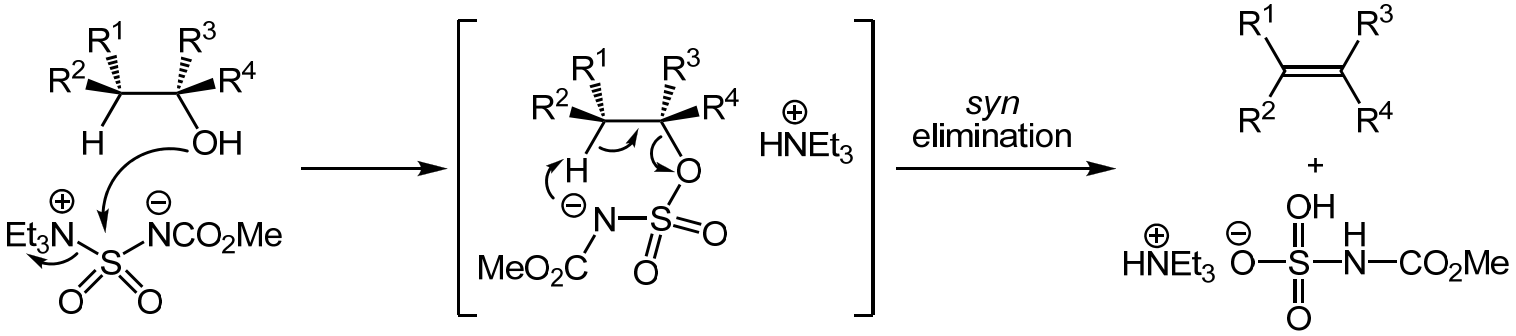
Burgess Dehydration

Preparation of Burgess Reagent



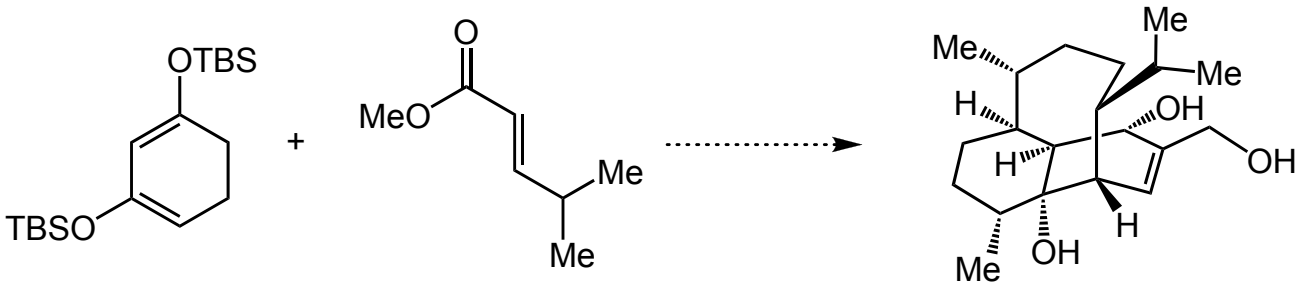
Burgess Dehydration





Summary

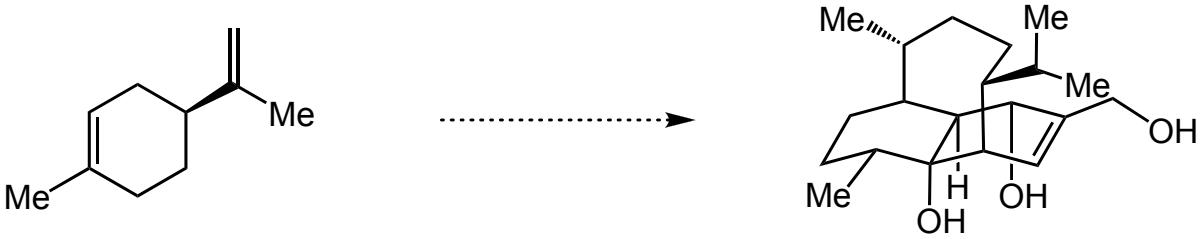
Baran's Group in 2009



Vinigrol

- Total synthesis, 23 steps, 2.7% overall yield
- **Grob fragmentation, Diels-Alder cycloaddition, dipolar cycloaddition, Shapiro reaction**

Luo's Group in 2019



(*S*)-(-)-Limonene

(-)-Vinigrol

- Scalable total synthesis, 20 steps, 1.4% overall yield, 605 mg
- **Anionic oxy-Cope rearrangement, hydroboration, Zweifel olefination, transannular DA**

The First Paragraph

First isolated from a fungal strain in Japan by Hashimoto and co-workers, vinigrol (**1**, Figure 1) occupies a special position in natural product small molecules. Among the structurally diverse terpenoids, vinigrol is the only one that is characterized by the 6−6−8 tricyclic ring system with the axial four-carbon tether bridging the densely decorated *cis*-decalin core. This natural product displays potent antihypertensive and platelet aggregation-inhibiting properties and has been reported as an antagonist for tumor necrosis factor α (TNF-α), which intrigues us the most.

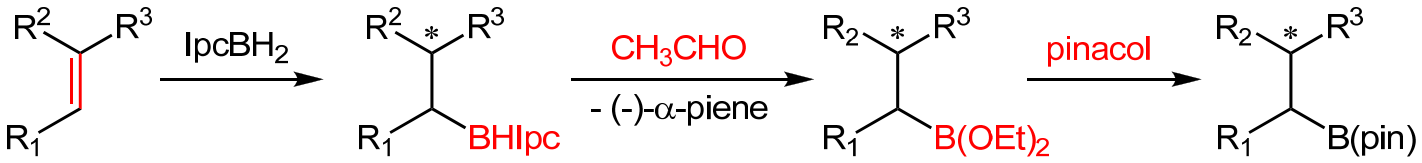
The Last Paragraph

In summary, we have developed a concise and scalable synthesis to accomplish (−)-vinigrol. Each step of this route has been optimized and validated on a gram-scale reaction whereas all the reagents shown in Scheme 1 were commercially available. But the synthetic approach is not without flaw. Even if the efficiency of our approach in terms of the overall steps is high (20 steps from *S*-limonene), the overall yield (1.4%) is lower than that of Baran's for racemic vinigrol (2.7%). If (+)-vinigrol is required, (*R*)-(+)-limonene would be needed. Nonetheless, our new strategy enabled the execution of carefully orchestrated transformations to construct such a strained framework and uniquely substituted stereogenic centers without the use of protecting groups. Investigation of the biological activities of (−)-vinigrol is ongoing, which will be reported in due course together with the evolution of our synthetic strategies.

Acknowledgement

Thanks
for your attention

Hydroboration with (+)-IpcBH$_2$



Renaud, P. et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 10858.