Literature Report IV

Total Synthesis of (+)-Pierisketone B

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Checker: Xin-Yu Zhan

Qi. G.; Walby G. D.; Wood M. D.; Martin S. F. *J. Am. Chem. Soc.* **2025**, *147*, 29631

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CV of Prof. Stephen F. Martin

Background:

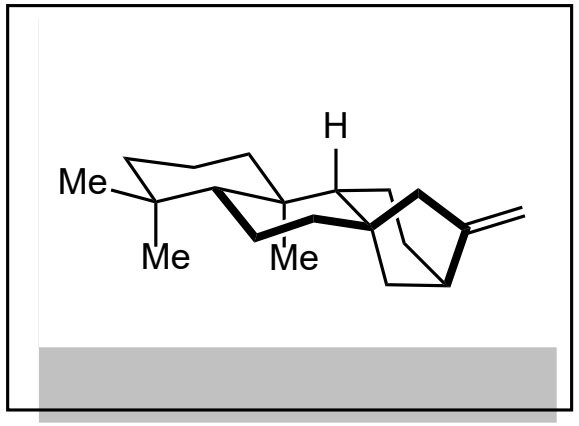
- **1964-1968** B.S., University of New Mexico
- **1968-1972** Ph.D., Princeton University
- **1972-1974** Postdoc., University of Munich and MIT
- **1974-Now** Professor, The University of Texas at Austin

Research Field:

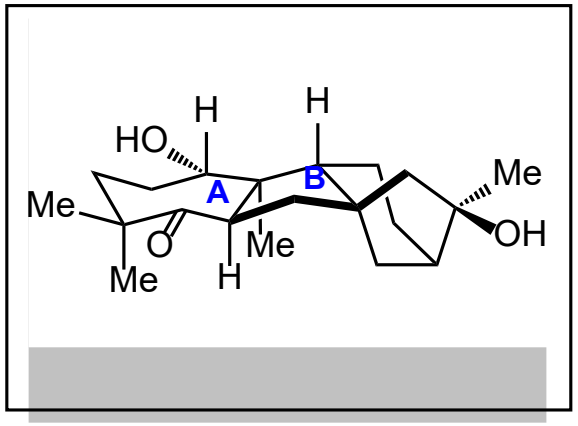
- Synthesis of Natural Products and Bioactive Compounds
- Molecular Recognition in Protein-Ligand Interactions

Contents

Introduction



***ent*-Kauranes**



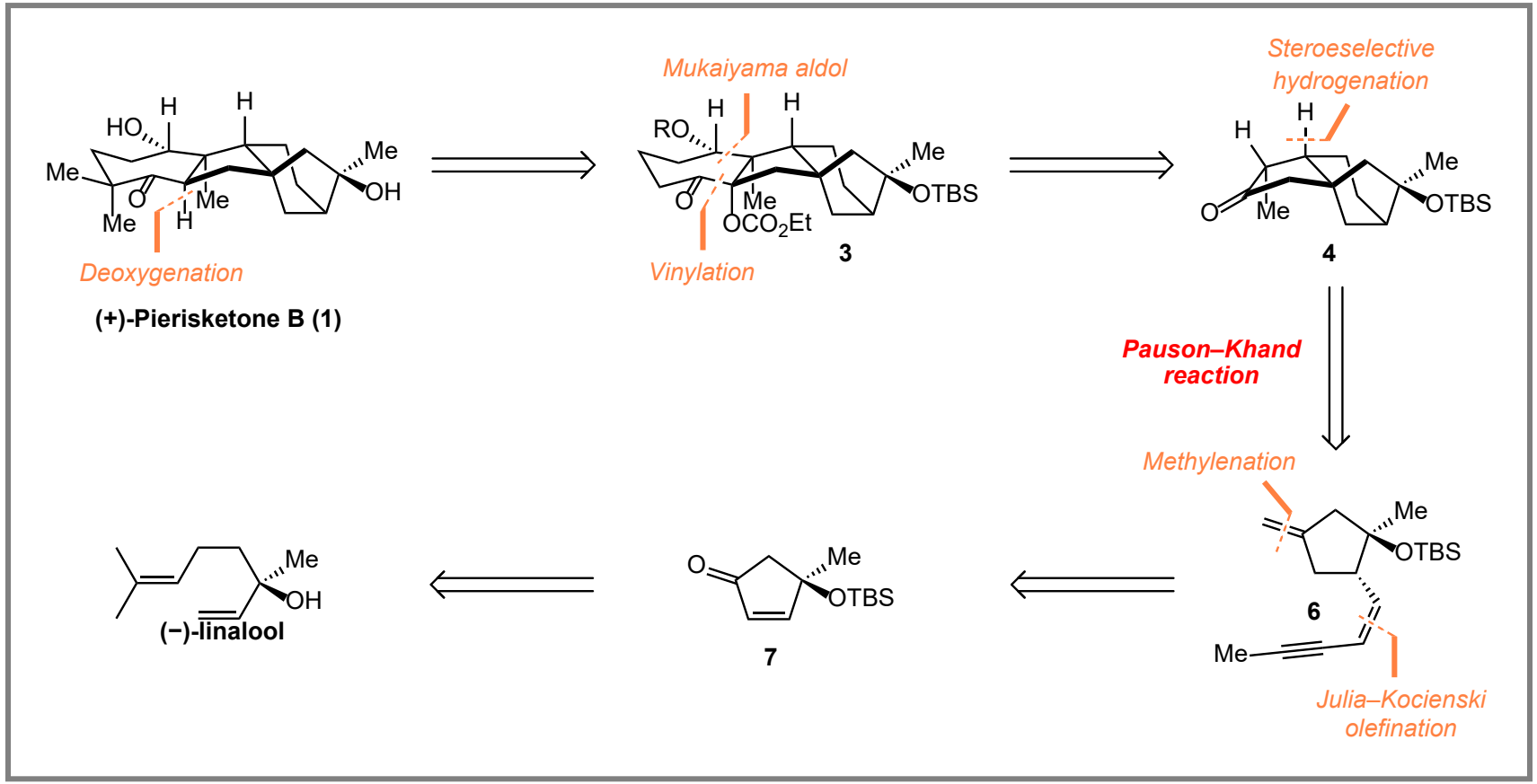
(+)-Pierisketone B

Pieris Formosa

- It was Isolated from Roots of *Pieris Formosa* in 2017;
- It Possesses an Unusual A-homo-B-nor-*ent*-Kaurane Framework;
- Unusual Molecular Architecture Paired with Significant Analgesic Activity.

Niu, C.-S.; Li, Y.; Liu, Y.-B.; Ma, S.-G.; Liu, F.; Wang, R.-B.; Qu, J.; Yu, S.-S.（庾石山）* *Org. Lett.* **2017**, *19*, 906

Retrosynthetic Analysis



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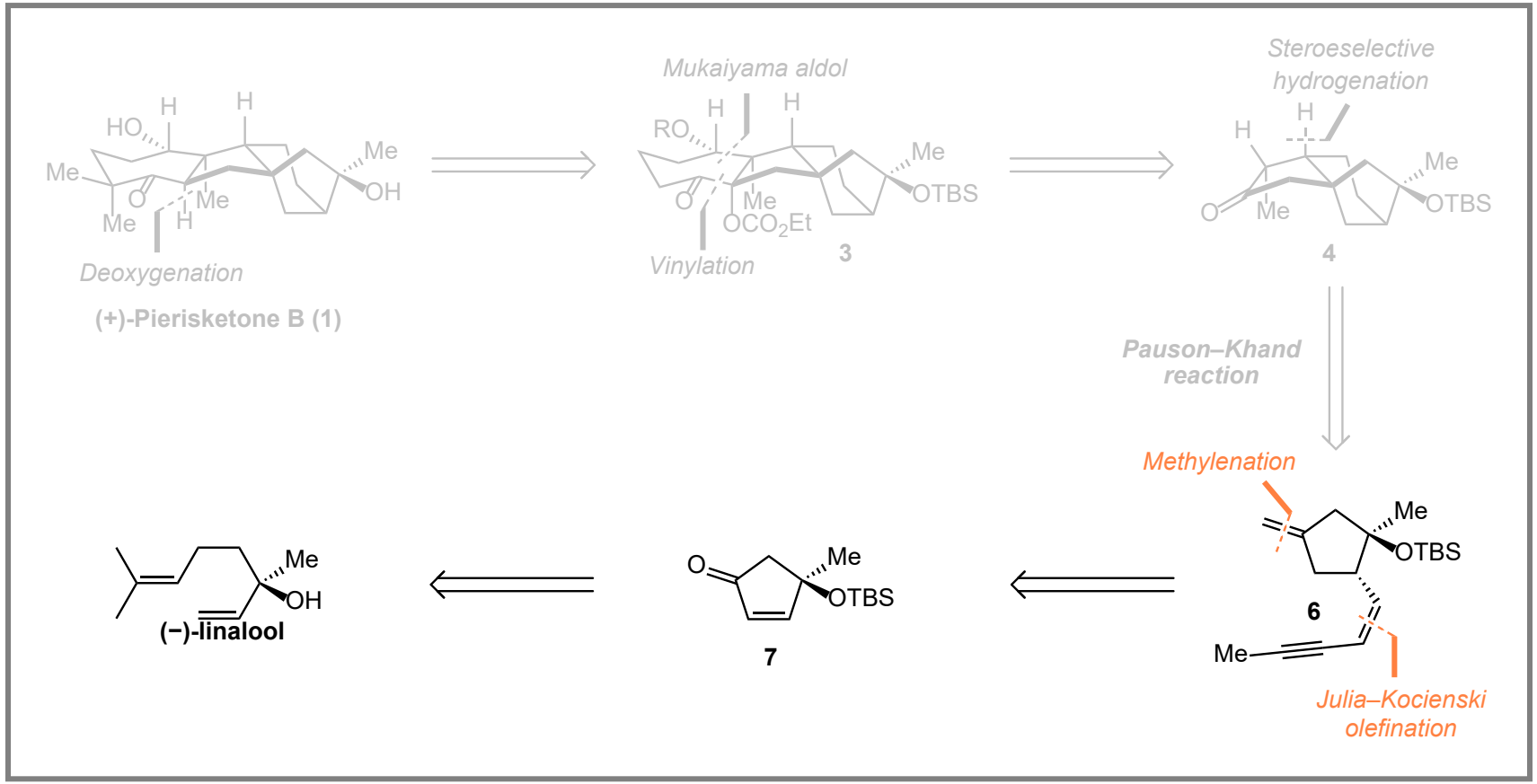
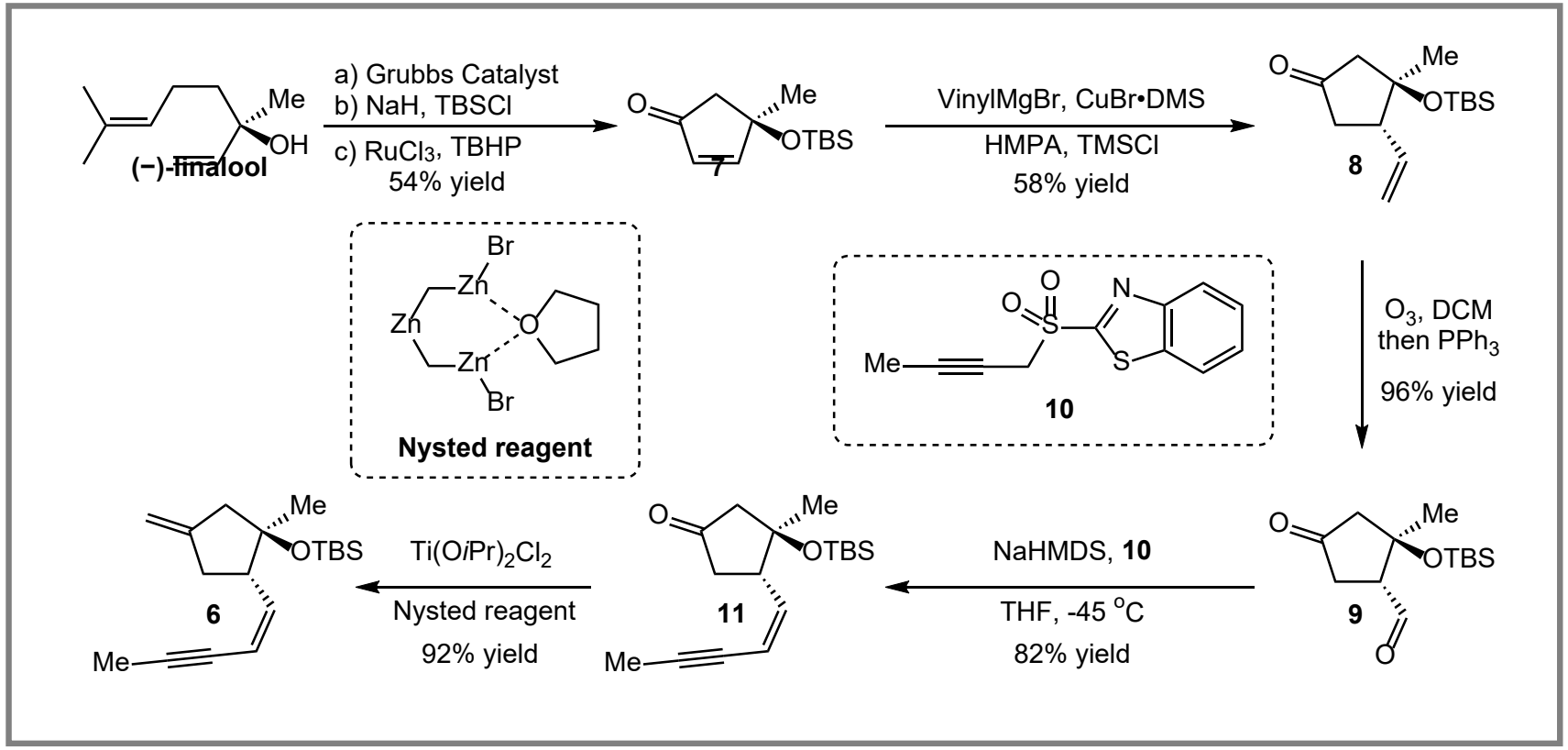


Synthesis of Compound 6



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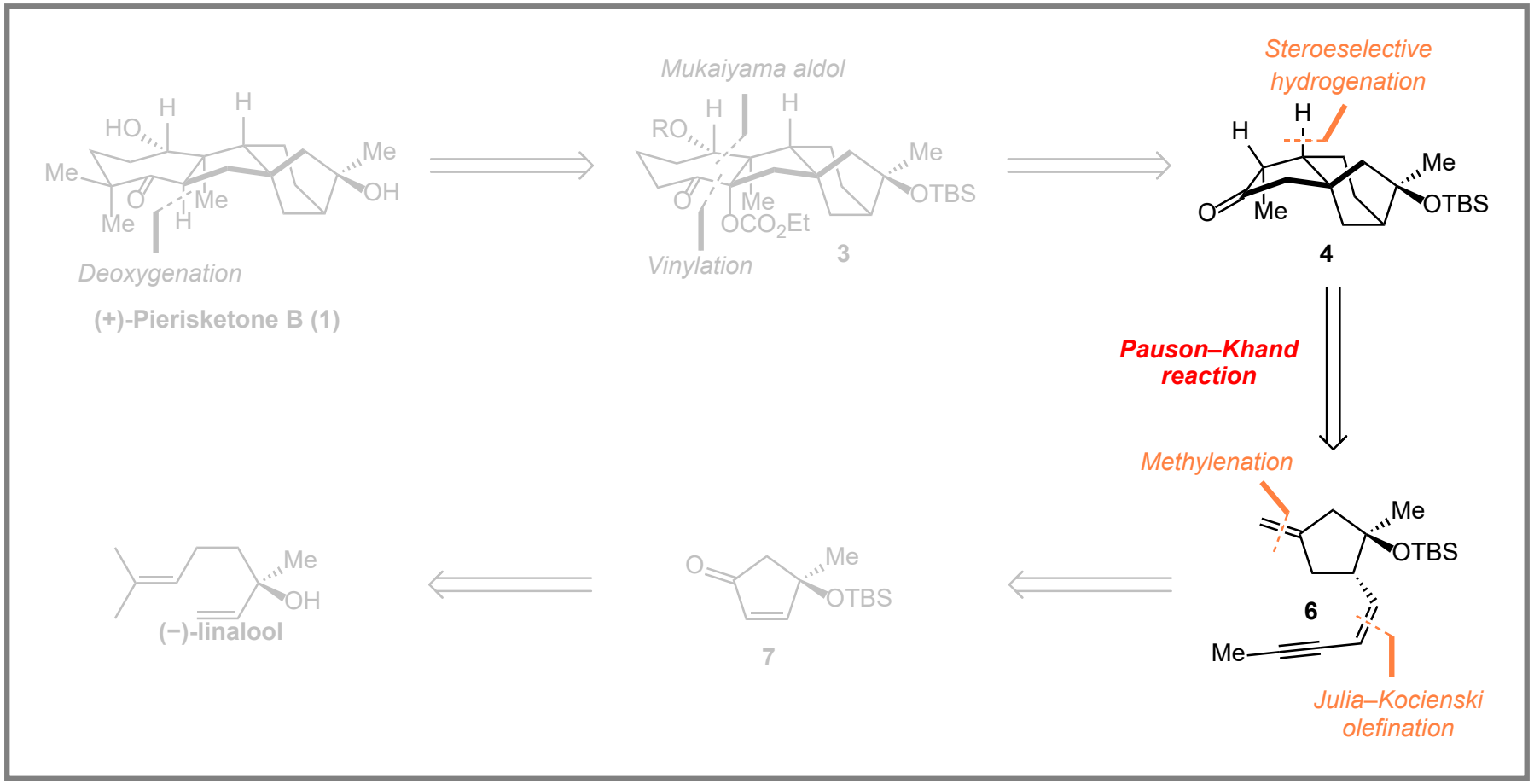
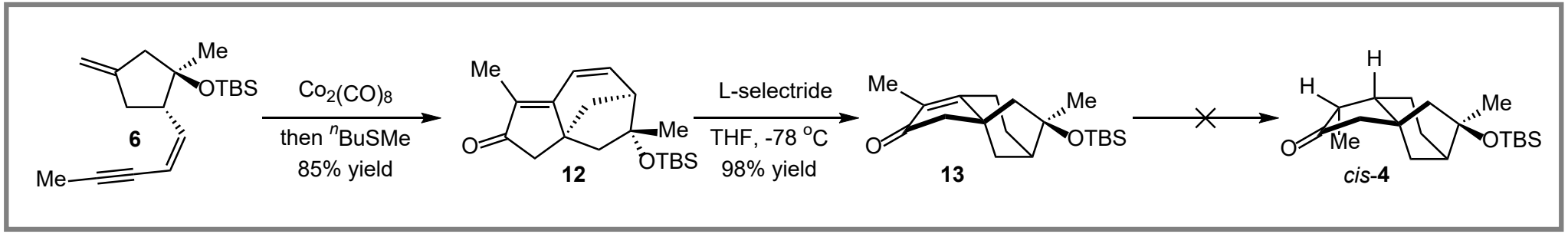
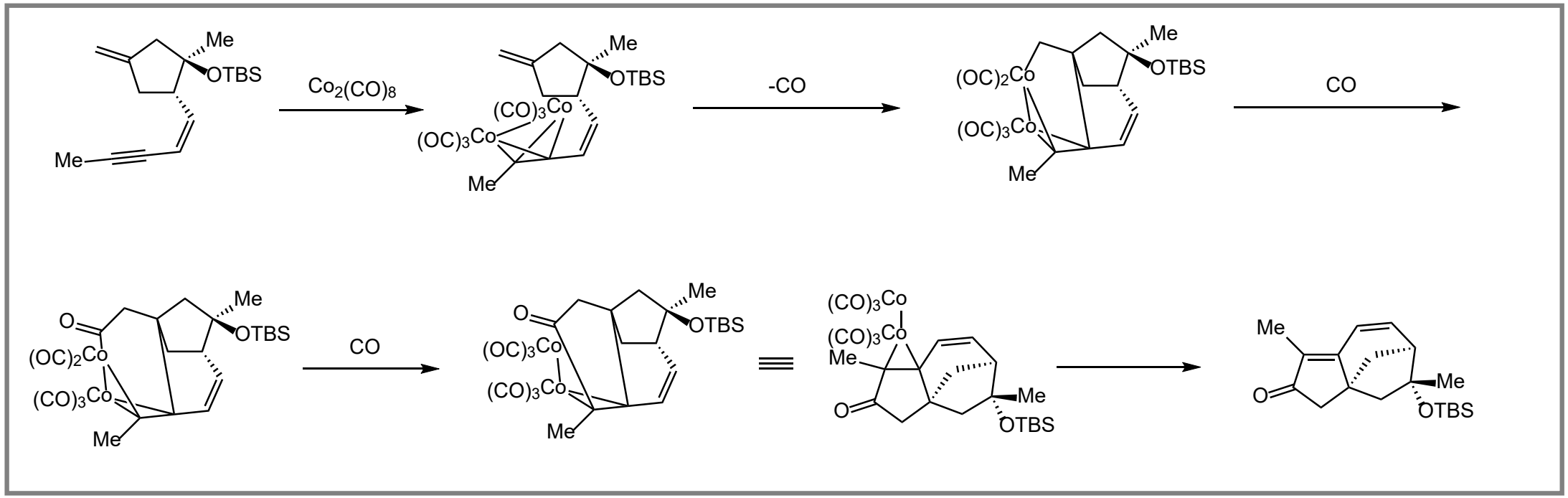
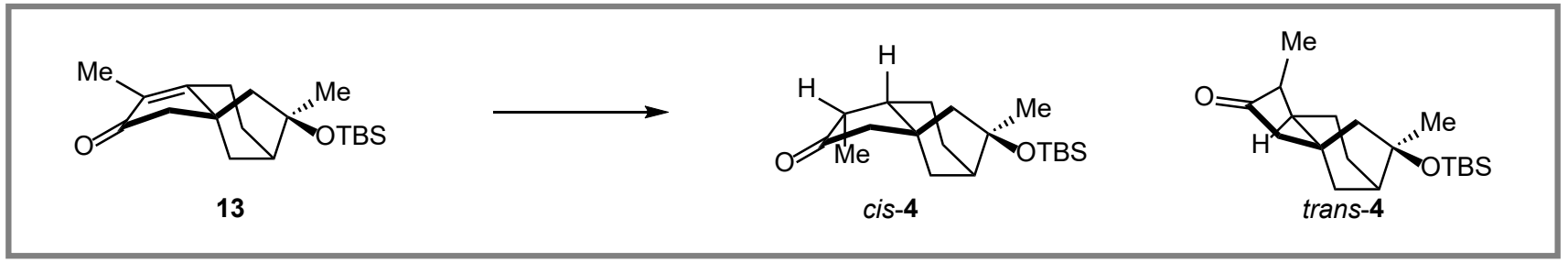


Synthesis of Compound 4



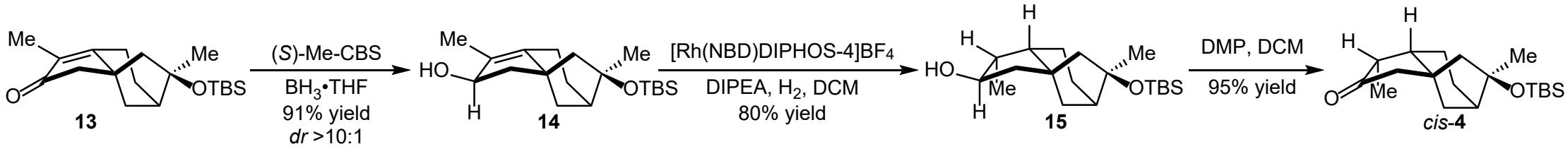


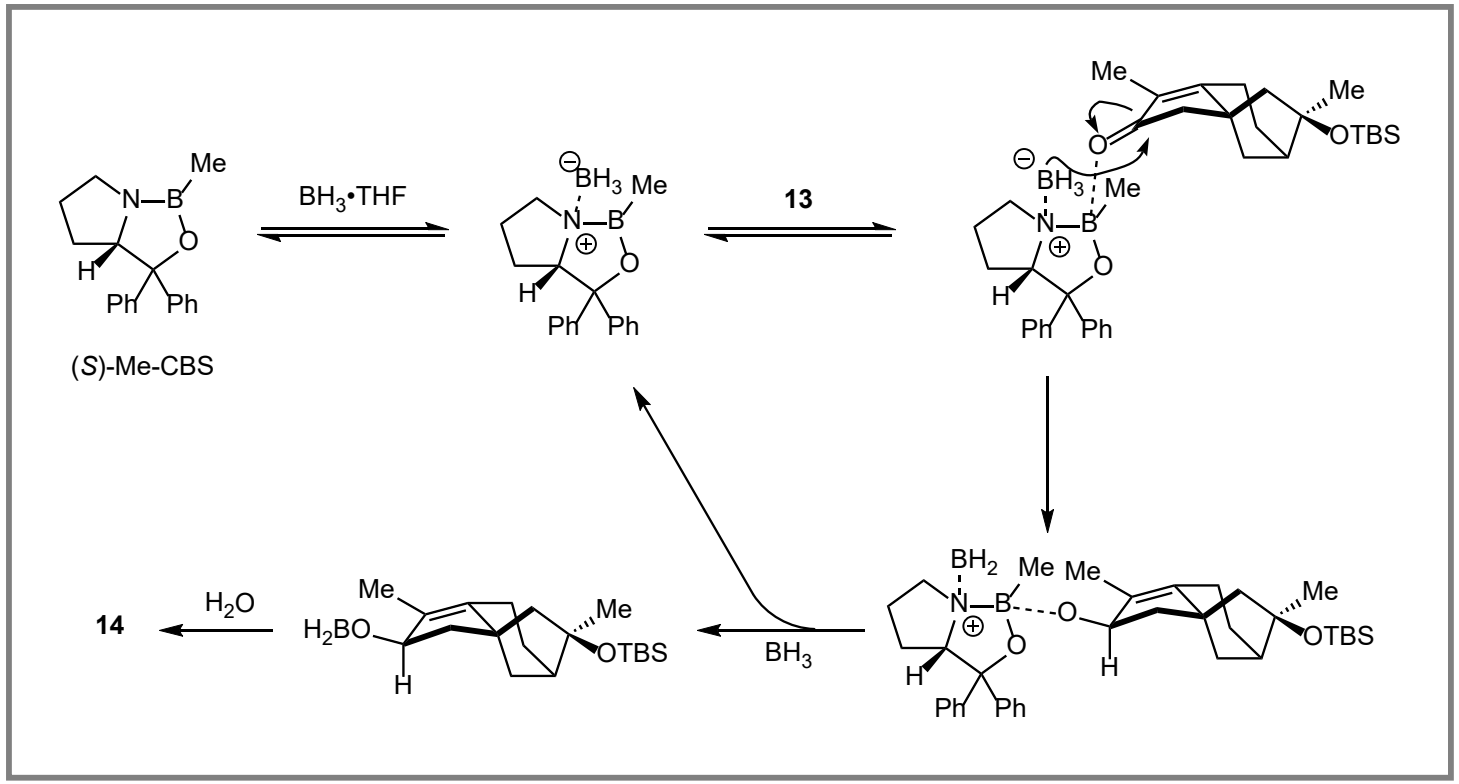
Synthesis of Compound 4



Entry	Condition	Yield (%)	*cis*:*trans*
1	Pd/C, H_2, Et_3N	95	1:30
2	Li, NH_3, ^tBuOH	67	1:4
3	NHC-CuCl, Ph_2SiH_2, PhMe	71	1:4
4	$Co(acac)_2$, $PhSiH_3$, TBHP, ^iPrOH	60	1:1
5	$Mn(dpm)_3$, $PhSiH_3$, TBHP, ^iPrOH	91	1:1

Synthesis of Compound 4





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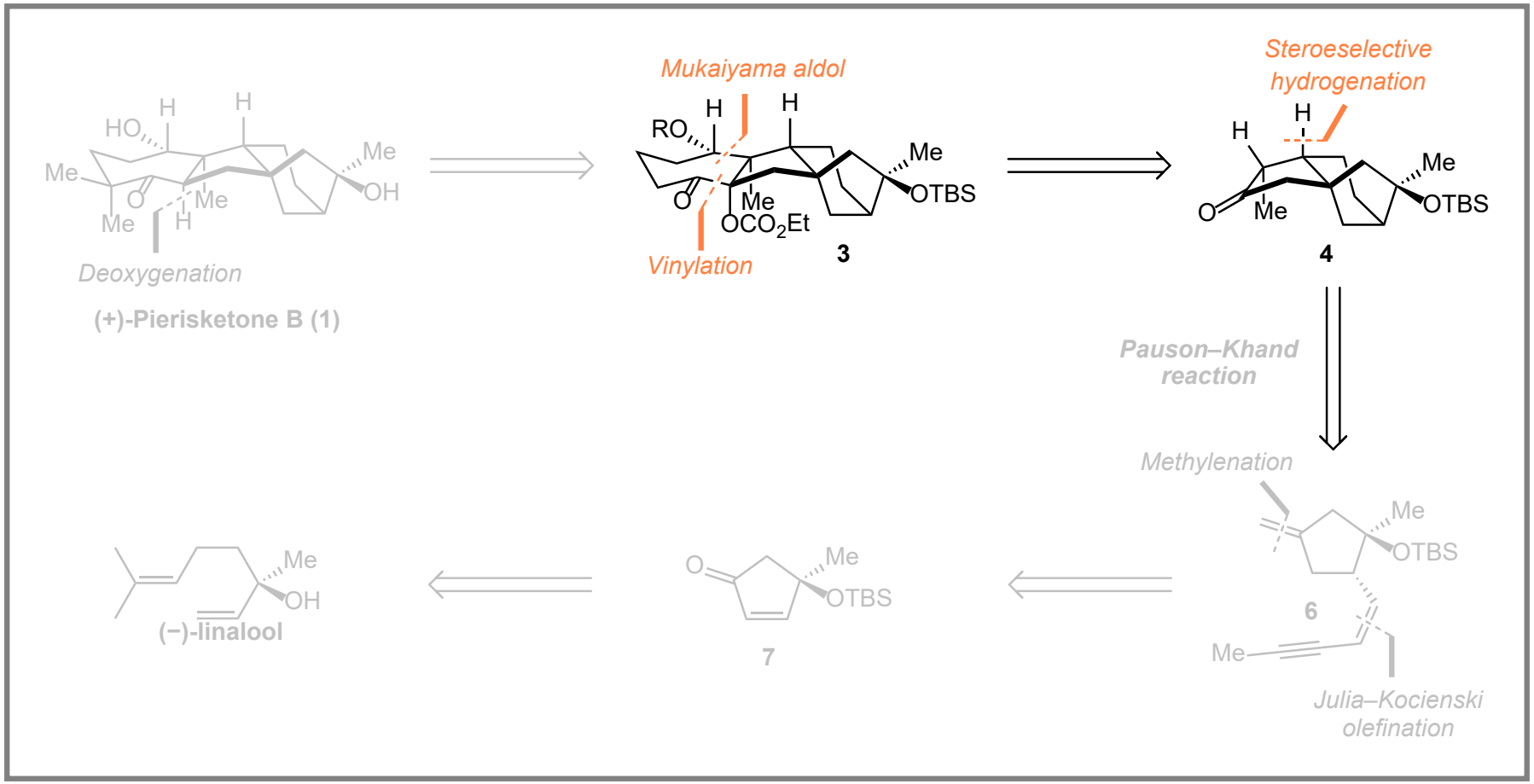
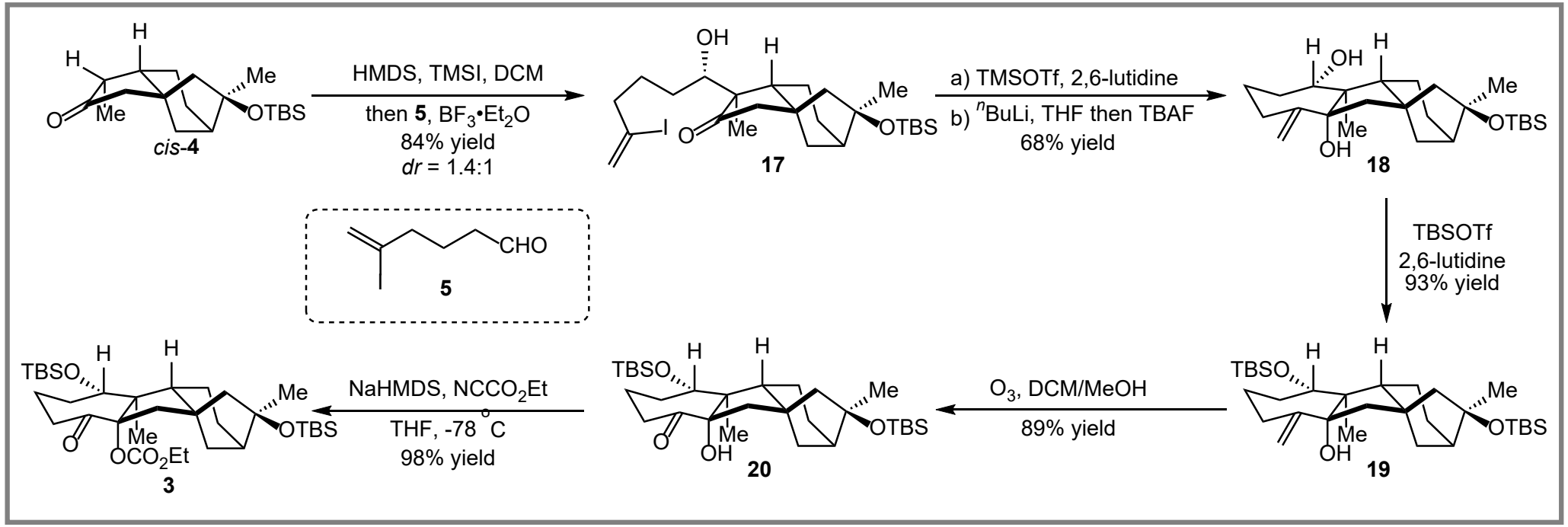


Synthesis of Compound 3



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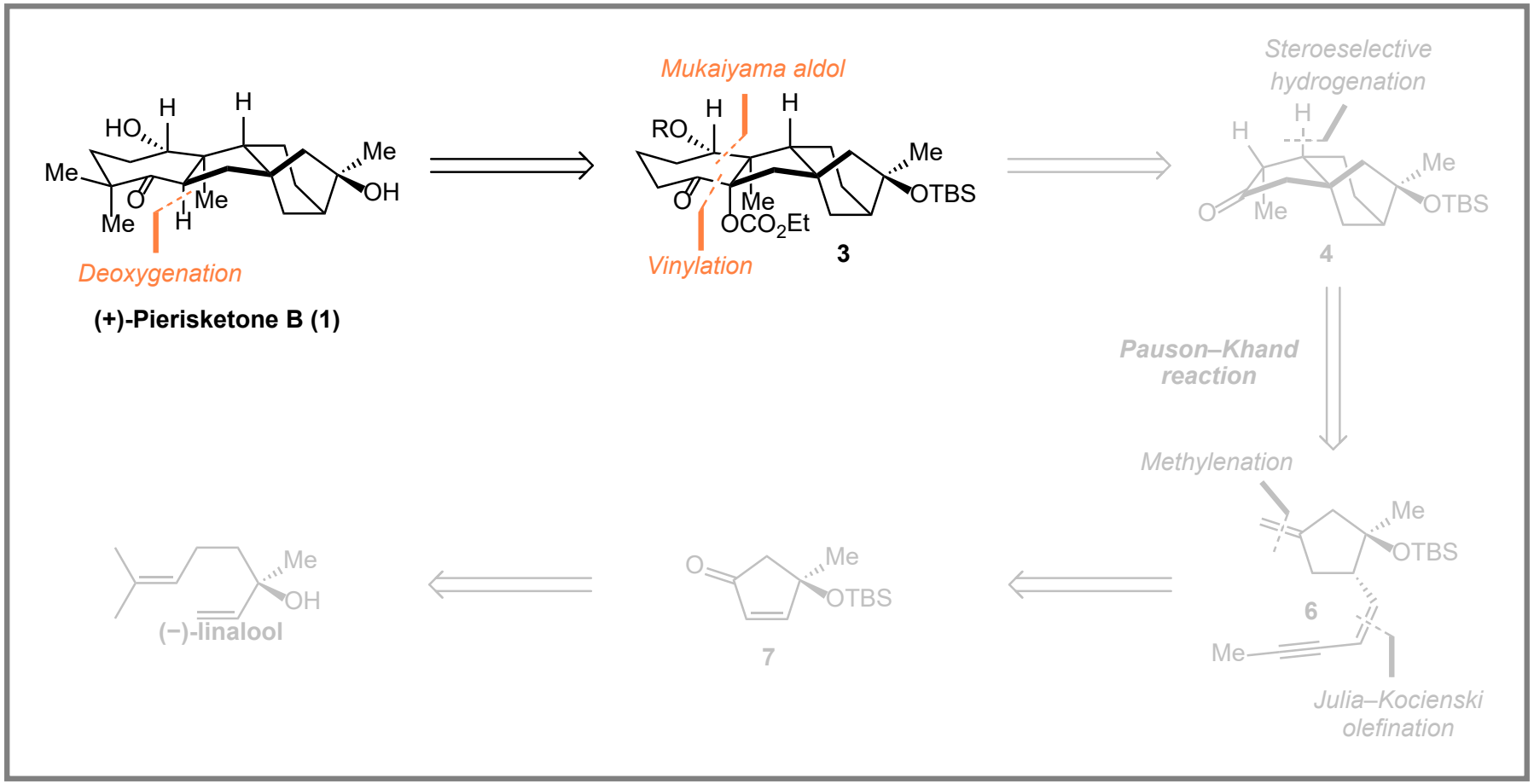
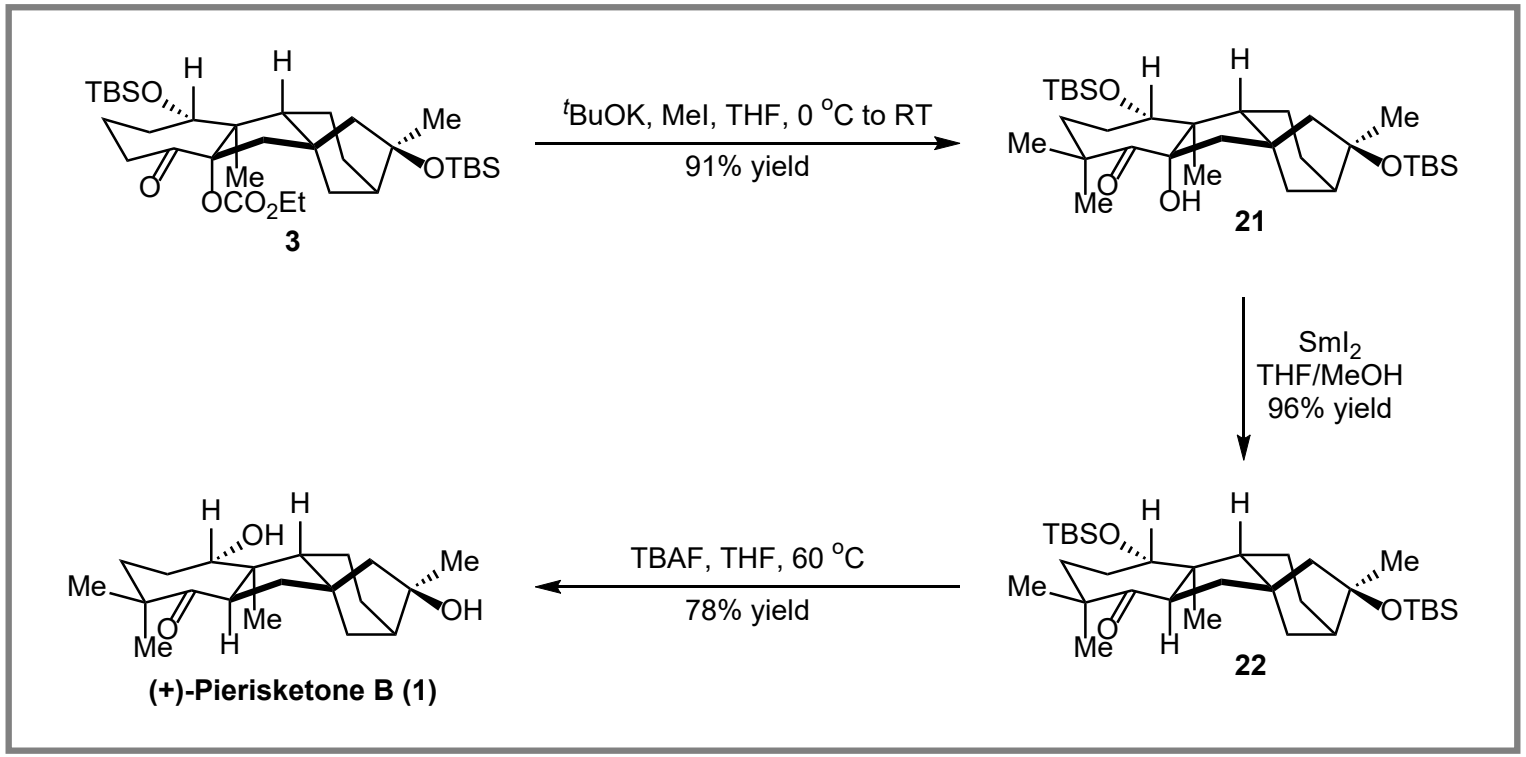
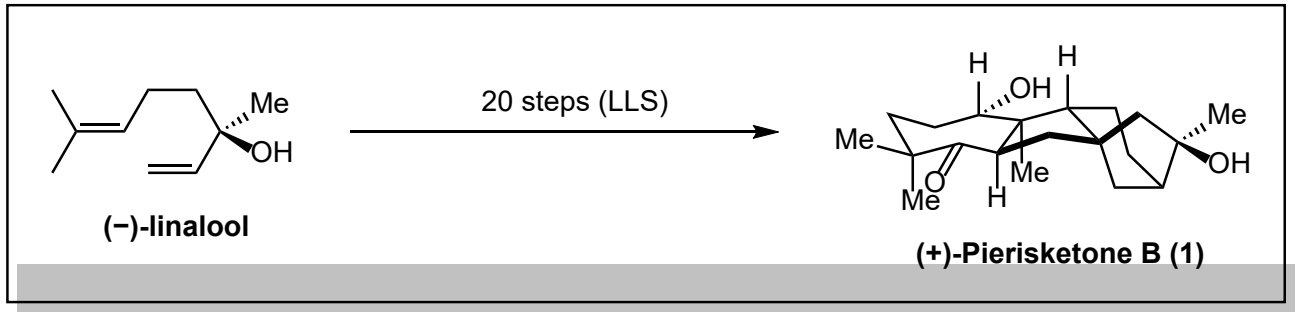


Synthesis of (+)-Pierisketone B



Summary



- Pauson-Khand Cyclization to Form the Bridged Tricyclic Core of Pierisketone B;
- Creation of the Requisite *cis*-fused Hydrindanone Moiety was Achieved by Hydroxyl Directed Hydrogenation of an Allylic Alcohol;
- Mukaiyama Aldol Reaction and Addition of a Vinyl Anion to a Proximal Ketone Group to Construct Unusual A-homo-B-nor-*ent*-Kaurane Framework.

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Writing Strategy

➢ **First Paragraph**

Biological Activity

↓

Unique Structure

↓

Challenge

- *ent*-Kaurane derived diterpenoids represent a large and structurally diverse group of terpene natural products. Their varied biological activities, which include antitumor, antibacterial and anti-inflammatory, and complex, polycyclic structures have attracted broad attention from the synthetic community.
- Unlike the related tetracyclic carbon scaffold of the grayanane diterpenoids, these natural products possess the unique pentacyclic 7/5/5/6/5 and tetracyclic 7/5/6/5 skeletons. Their unusual molecular architecture paired with significant analgesic activity make Pierisketone B intriguing targets for total synthesis.
- The polycyclic structures and numerous stereochemical complexities, including three quaternary carbon atoms and five contiguous chiral centers, found in pierisketone B pose significant challenges.

Writing Strategy

➢ **Last Paragraph**

Summary

Key Steps

Prospect

- In summary, we completed the first total synthesis of (+)-pieri-sketone B in 18 steps (3.4% overall yield) from the known enone , which is available in two steps from (−)-linalool.
- The synthesis featured an unusual PKR to form 12, which comprises the bridged tricyclic core of 1. The next key step was the hydroxy-group directed hydrogenation of the allylic alcohol 14 that led to the key intermediate cis-4. Subsequent annulation of the A ring onto cis-4 to provide 18 was achieved via a sequence involving a Mukaiyama aldol reaction ……
- Lessons learned from these investigations will enable future syntheses of pierisketolide A and related diterpenes.

Representative Examples

- Despite the lack of diastereoselectivity in the Mukaiyama reaction, sufficient quantities of **17** were readily accessible for elaboration of the A ring.(*n*.详尽阐述，细化)

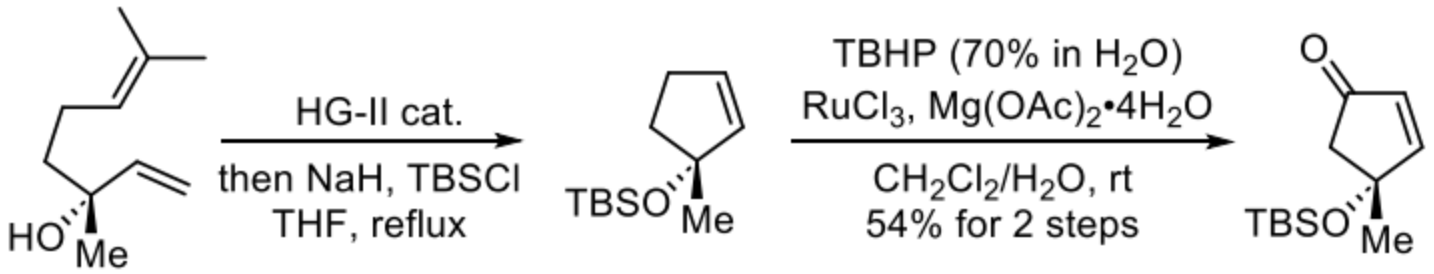
- The solution to our dilemma was revealed by a serendipitous discovery made during a separate series of experiments directed toward the synthesis of pierisketolide A. (*adj*.侥幸的，凑巧的)

- To address the various problems associated with their synthesis, we developed a divergent plan wherein both pierisketone B (1) and pierisketolide A (2) could arise from the pivotal intermediate 3. (*adj*. 中枢的，关键的)

Acknowledgement

Thank You for Your Attention!

Synthesis of 7



Julia-Kocienski Olefination