

Literature Report IX

Enantiocontrolled Total Synthesis of (-)-Retigeranic Acid A

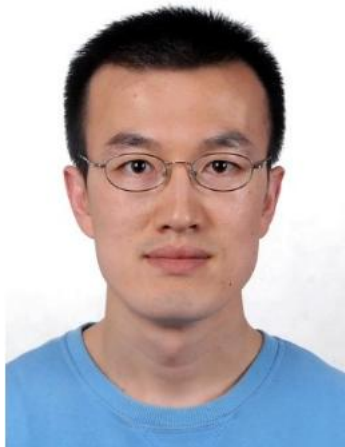
Reporter: Yu-Qing Bai

Checker: Zheng Liu

Date: 2023-07-24

Chen, X.; Wang, S.-H. *et al. J. Am. Chem. Soc.* **2023**, *145*, 13549

CV of Prof. Shao-Hua Wang



Background:

- ❑ 1997-2001 B.S., Lanzhou University
 - ❑ 2001-2006 Ph.D., Lanzhou University
 - ❑ 2006-2011 Postdoc., Mayo Clinic
 - ❑ 2011-2017 Associate Professor, Lanzhou University
 - ❑ 2017-now Professor, Lanzhou University
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Research:

- Design and synthesis of small molecules with biological (drug) activity;
- Total synthesis of natural pharmaceutical molecules.

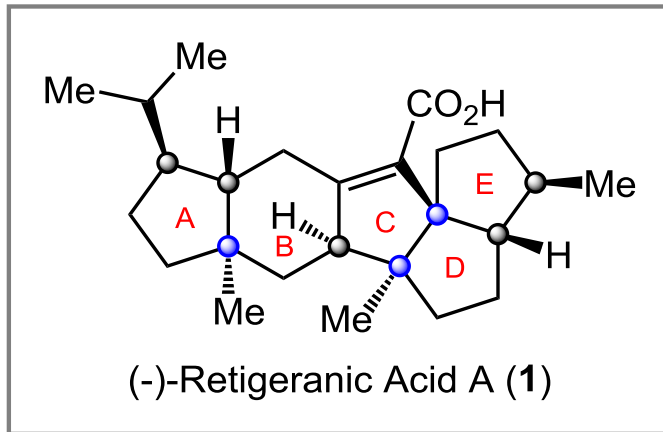
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2 Asymmetric Total Synthesis of (-)-Retigeranic Acid A

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Introduction



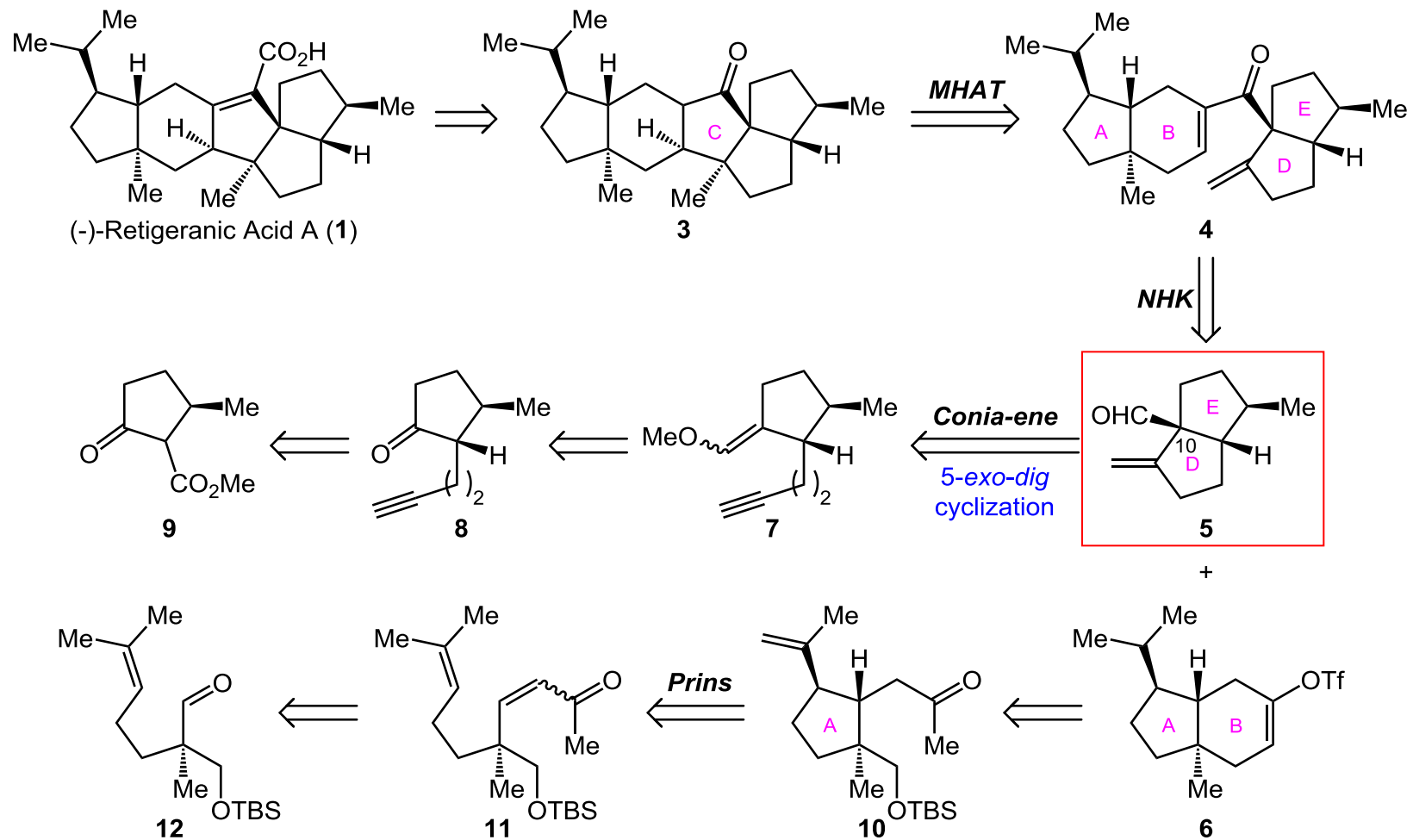
Lobaria retigera

- It was first isolated from Himalaya lichens of *Lobaria retigera* in 1965 and characterized in 1974;
- It features an angular triquinane subunit and a *trans*-hydrindane fused pentacyclic scaffold that contains eight stereogenic centers;
- The biological activities of retigeranic acid A (1) have not been determined.

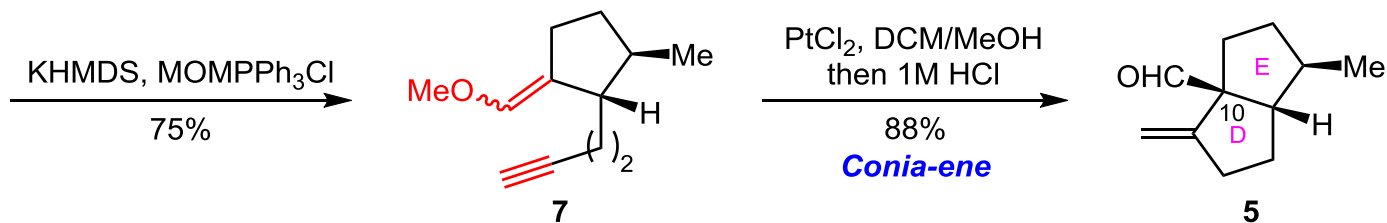
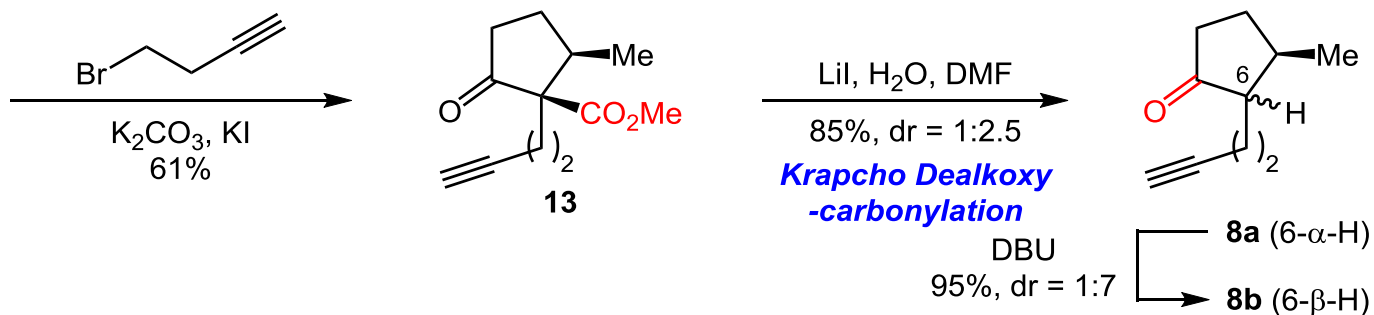
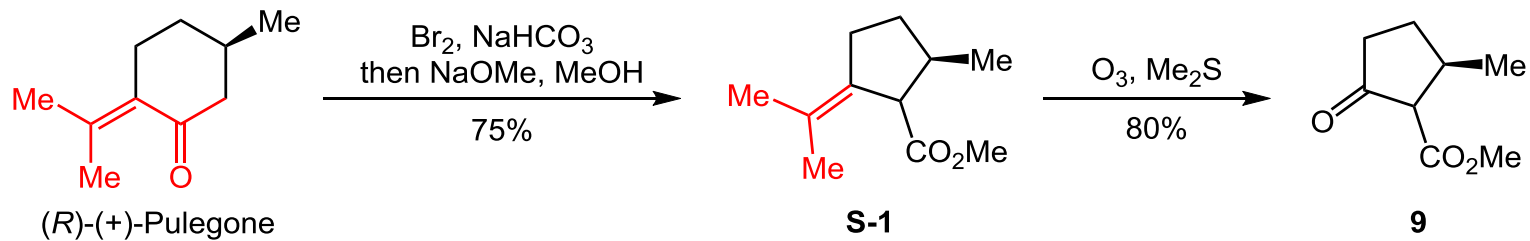
Seshadri, T. R. *et al. Curr. Sci.* **1965**, 34, 9

Shibata, S. *et al. Acta Crystallogr., Sect. B: Struct. Cycstallogr. Cryst. Chem.* **1974**, 30, 358

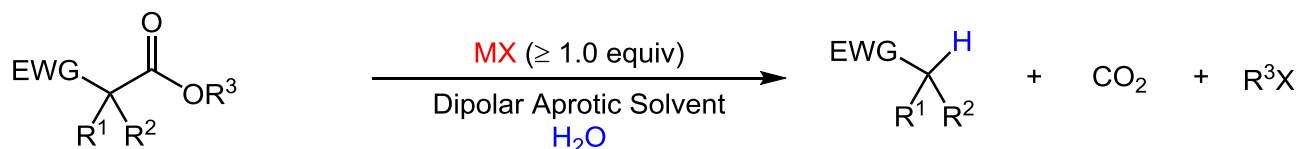
Retrosynthetic Analysis



Stage 1: Synthesis of 5



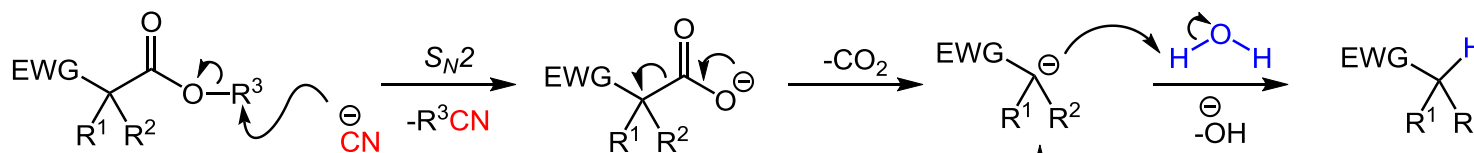
Krapcho Dealkoxycarbonylation



EWG = CO₂R, SO₂R, COR, CN
 R¹⁻² = H, alkyl, aryl
 R³ = Me, Et

MX = NaCN, KCN, LiCl, NaCl...

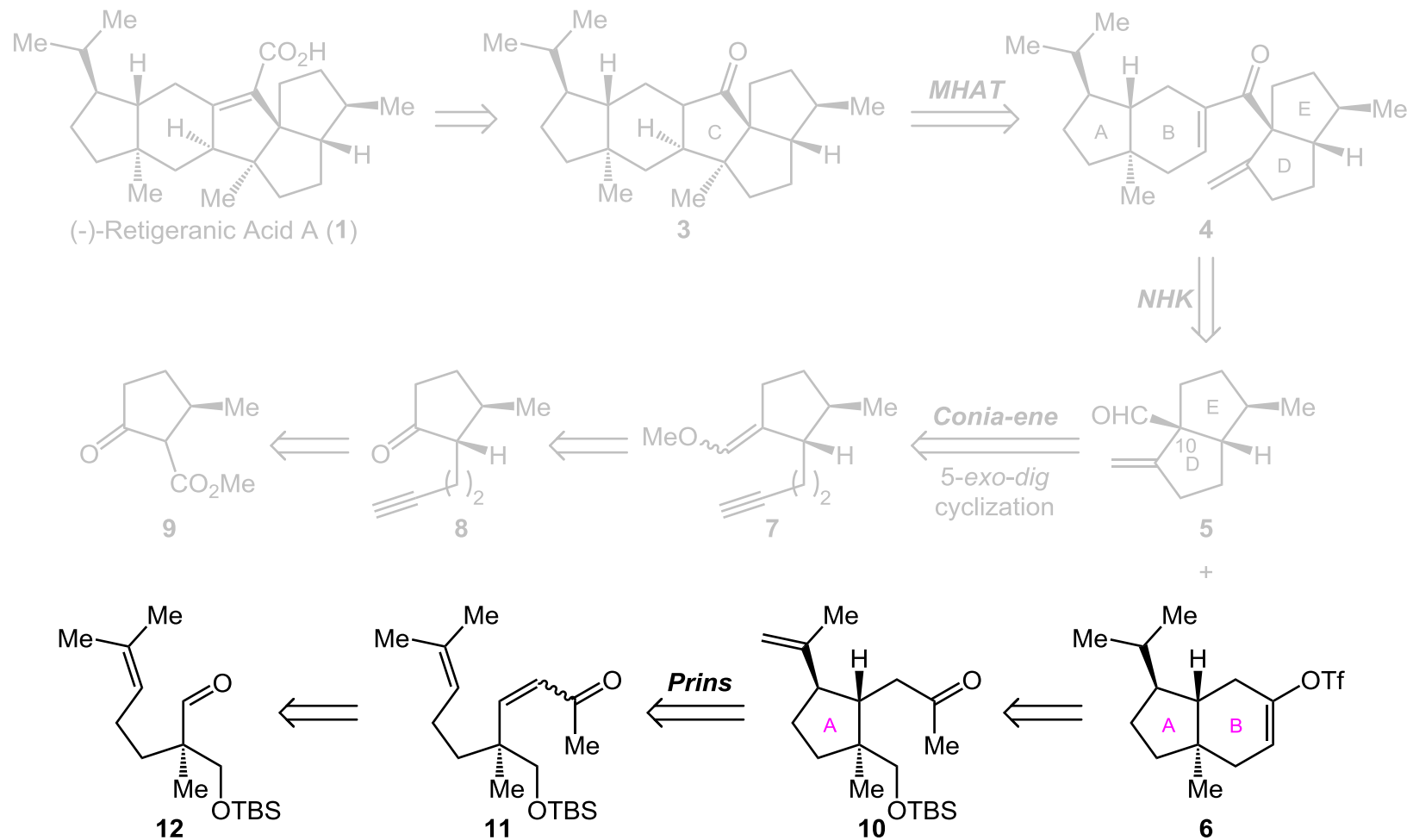
α,α -Disubstituted Ester



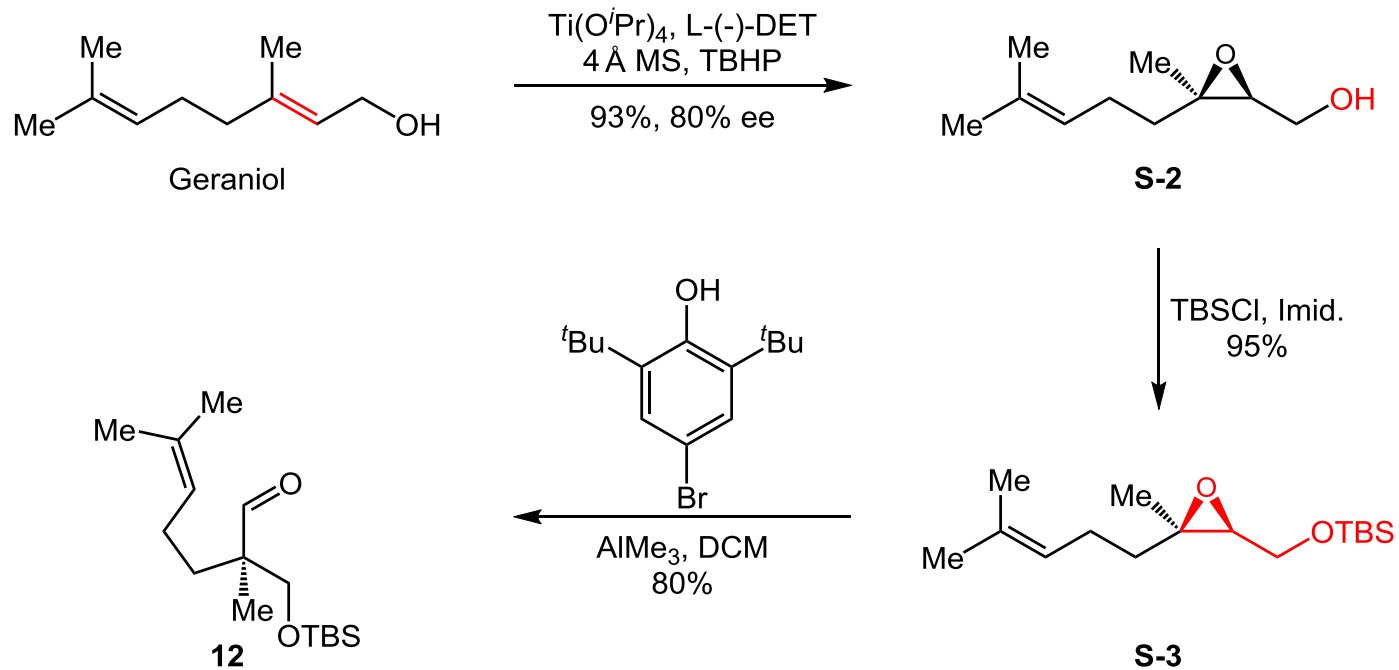
α -Monosubstituted Ester (R² = H)



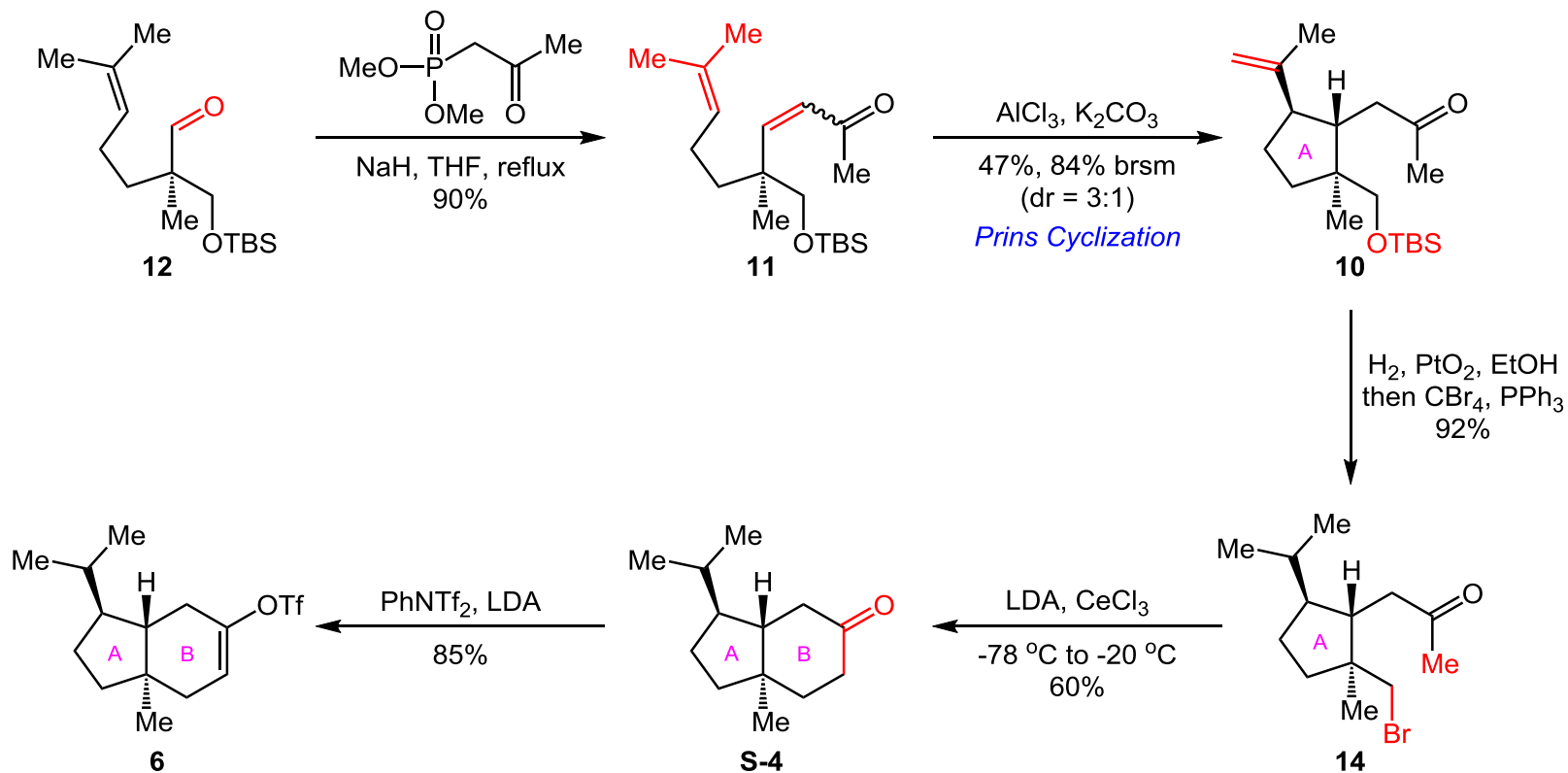
Stage 2: Synthesis of 6



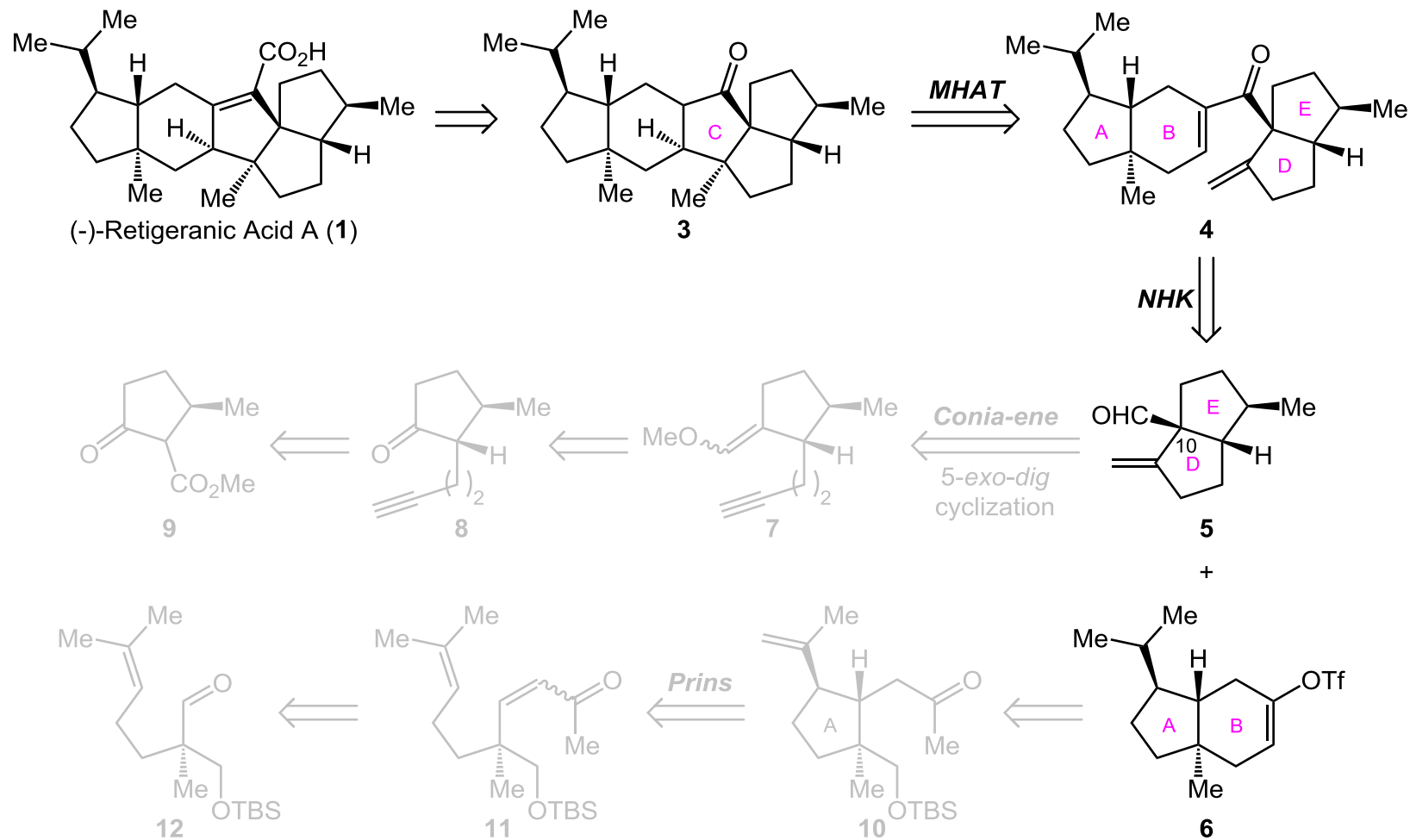
Synthesis of 12



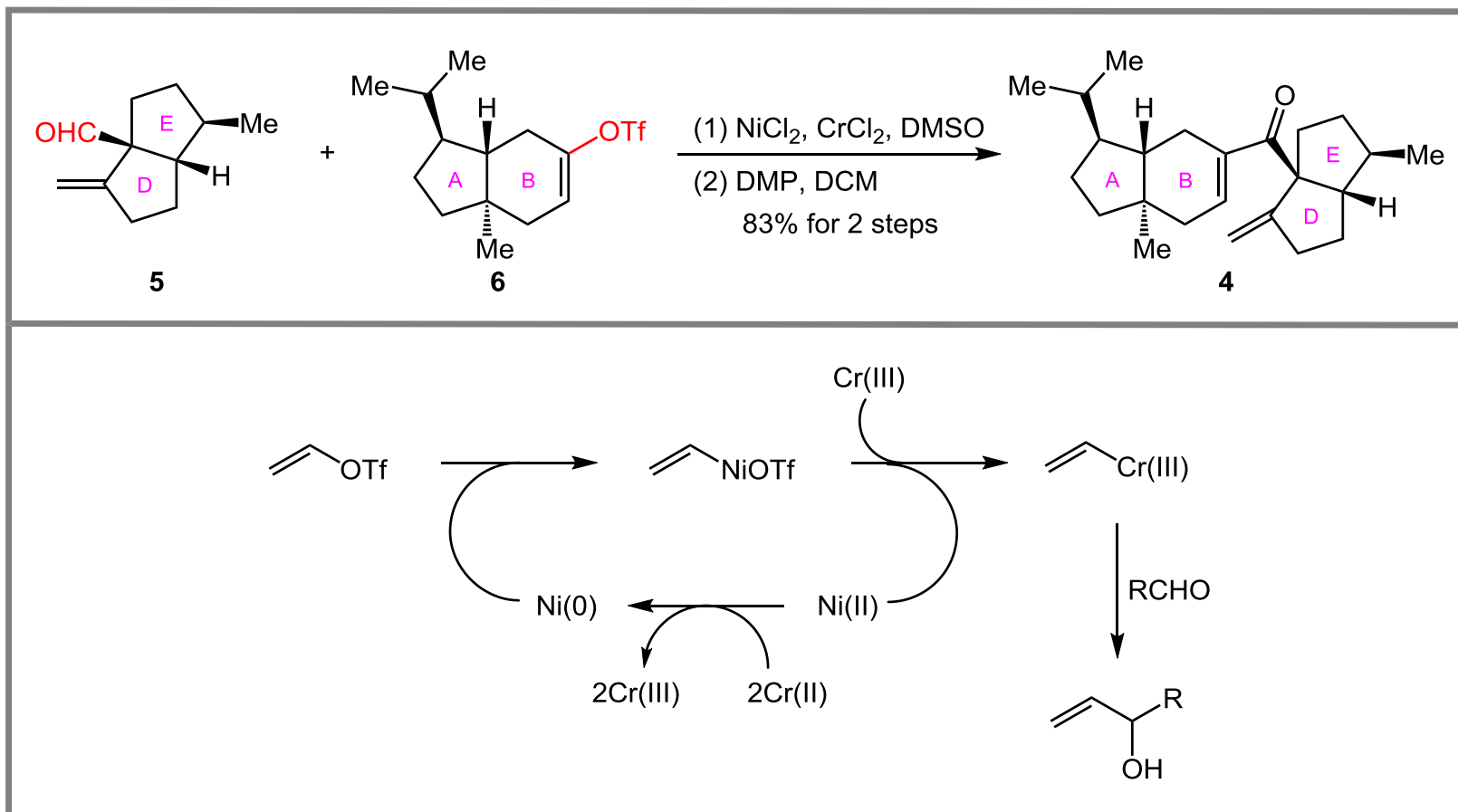
Synthesis of 6



Stage 3: Synthesis of (-)-Retigeranic Acid A (1)

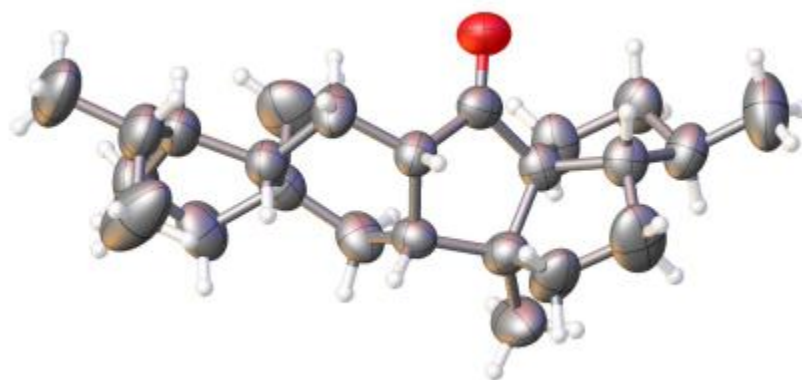
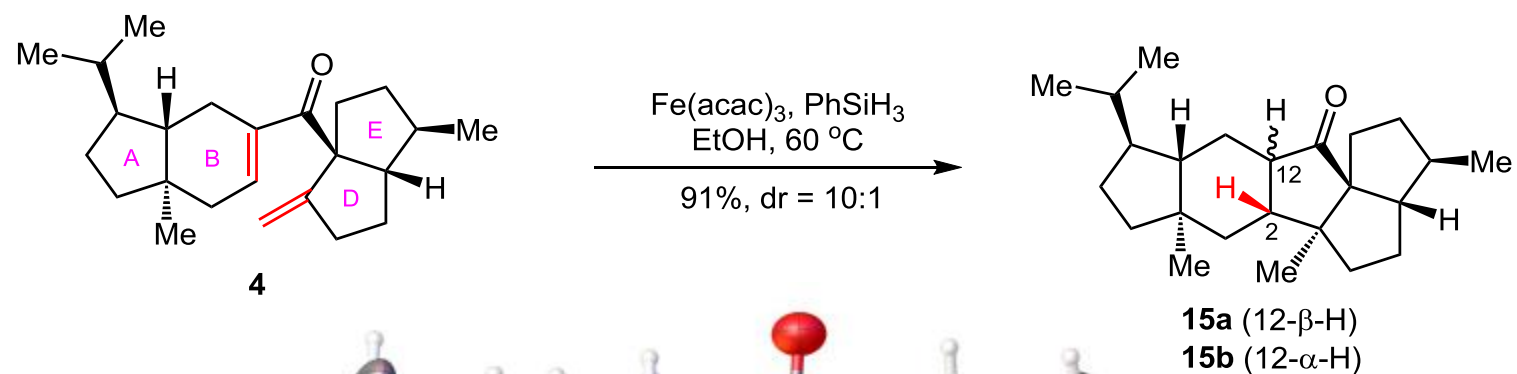
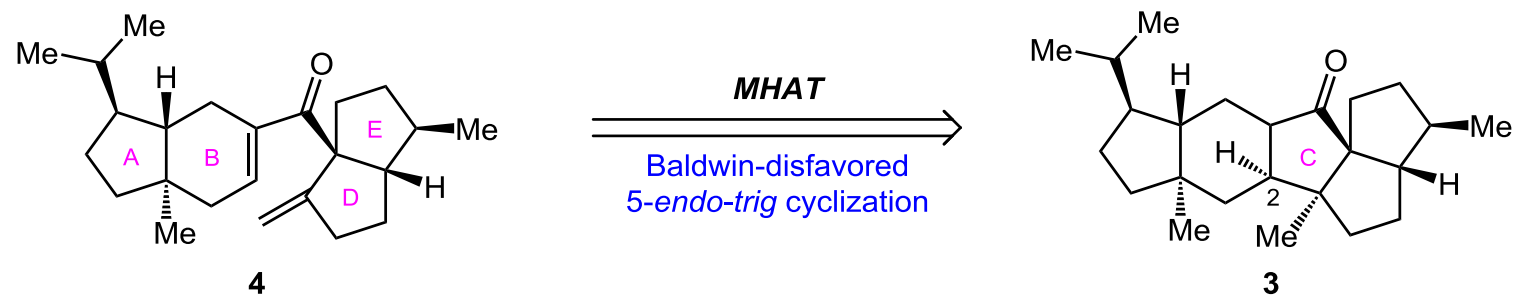


Nozaki-Hiyama-Kishi (NHK) Coupling



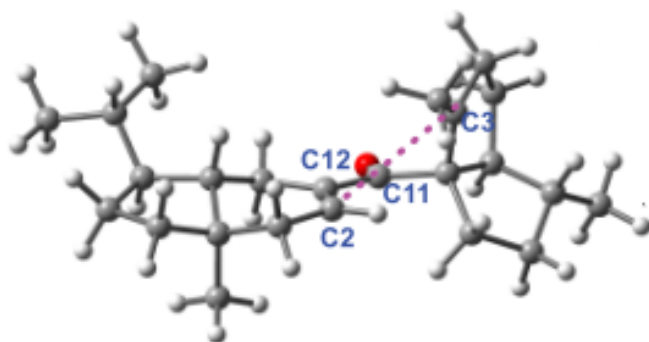
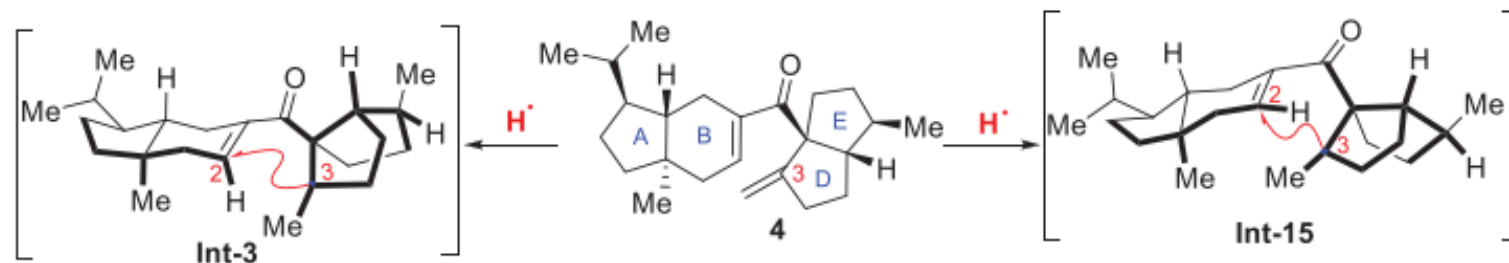
Takai, K.; Nozaki, H. *et al. J. Am. Chem. Soc.* **1986**, *108*, 6048

Diastereoselective MHAT Cyclization



X-ray structure of **15a**

DFT Calculations

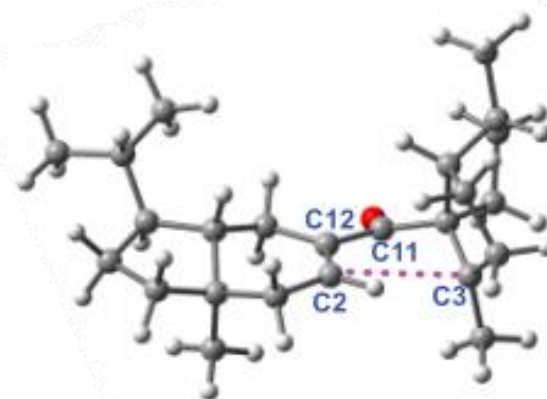


$$\tau_{(C11-C12-C2-C3)} = 31.9^\circ$$

$$d_{C2-C3} = 3.5 \text{ \AA}$$

$$\Delta G_{\text{Int-3}} = 1.5 \text{ kcal/mol}$$

$$P_{\text{Int-3}} = 0.3\%$$



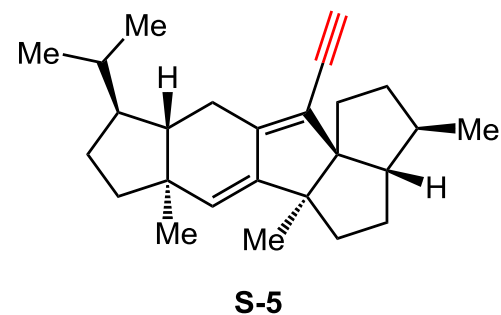
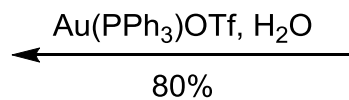
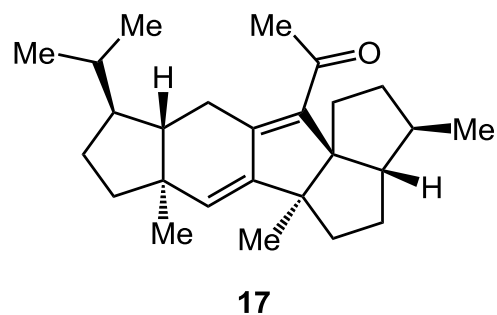
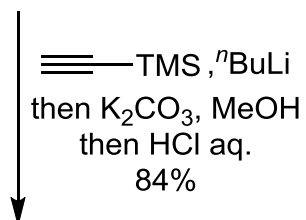
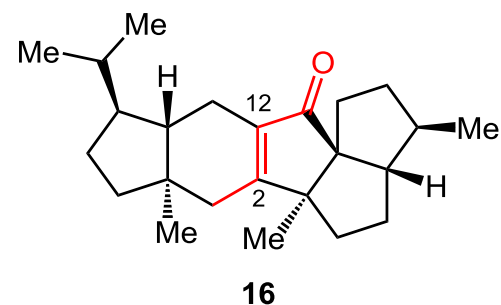
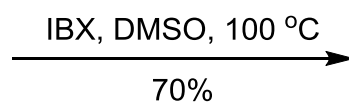
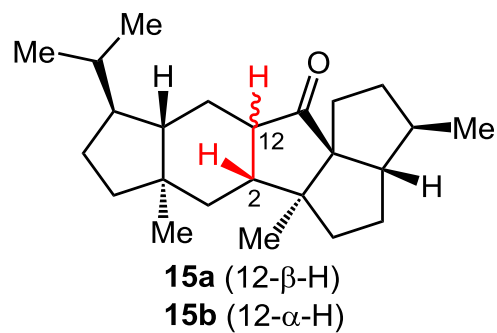
$$\tau_{(C11-C12-C2-C3)} = 0.2^\circ$$

$$d_{C2-C3} = 3.1 \text{ \AA}$$

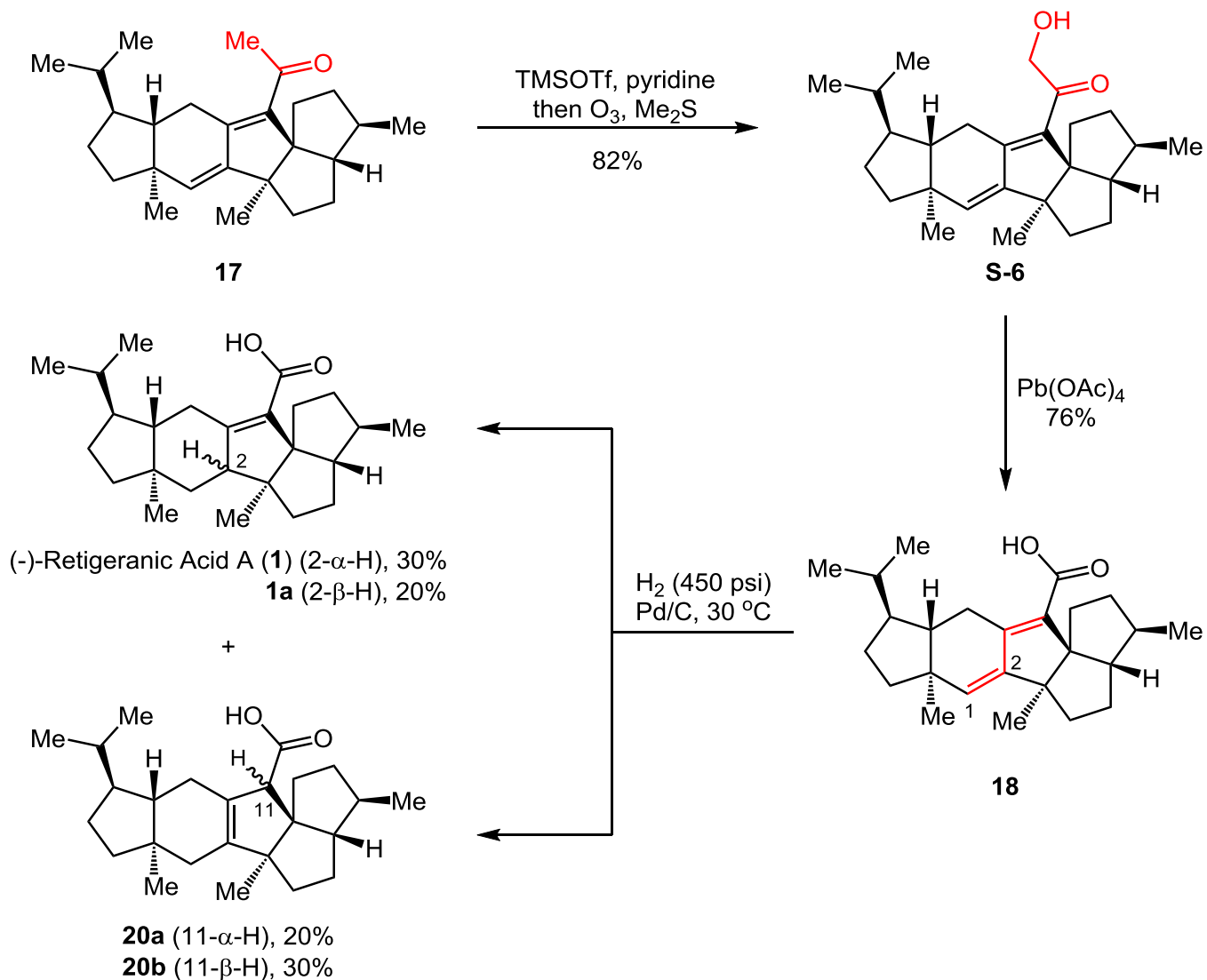
$$\Delta G_{\text{Int-15}} = 0 \text{ kcal/mol}$$

$$P_{\text{Int-15}} = 99.7\%$$

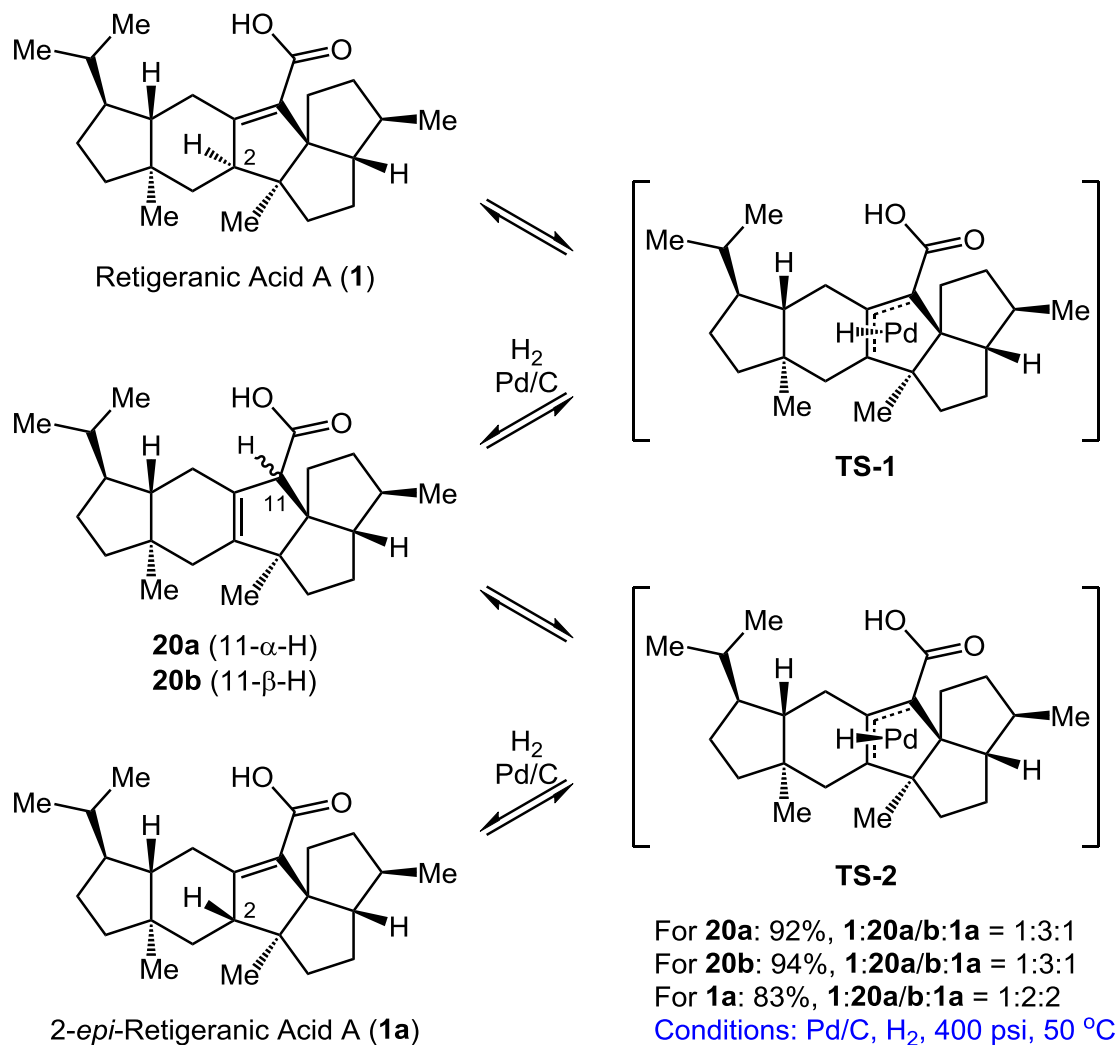
Synthesis of 17



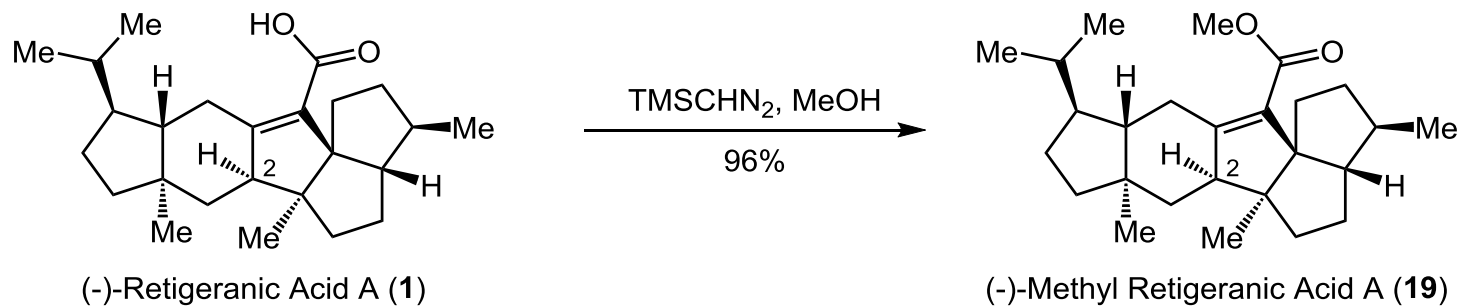
Synthesis of (-)-Retigeranic Acid A (1)



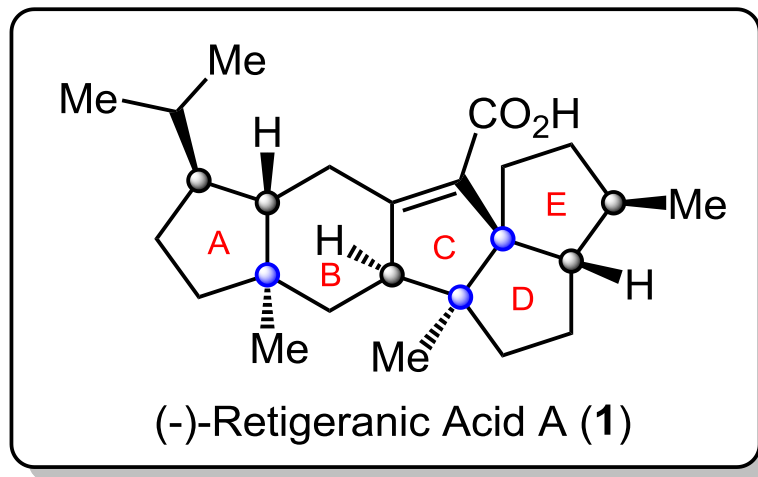
Synthesis of (-)-Retigeranic Acid A (1)



Synthesis of (-)-Methyl Retigeranic Acid A (19)



Summary



- 18 linear steps from Geraniol, 1.2% overall yield;
- Pt-catalyzed Conia-ene 5-*exo-dig* cyclization;
- Intramolecular diastereoselective Prins cyclization;
- Intramolecular MHAT-mediated Baldwin-disfavored 5-*endo-trig* radical cyclization.

The First Paragraph

Writing strategy

**Source and
bioactivities of
retigeranic acid A**



**Structural features of
retigeranic acid A**

- ❑ Retigeranic acid A, a sesterterpene first isolated from Himalaya lichens of *Lobaria retigera* as a mixture with retigeranic acid B...the significant bioactivities of its parent genus *Lobaria* have been supported by the utility in treating eczema and lung disorders as a traditional medicine.
- ❑ Retigeranic acid A possesses an angular triquinane subunit and a *trans*-hydrindane fused pentacyclic scaffold that contains eight stereogenic centers.

The Last Paragraph

Writing strategy

Summary of this work



**Prominent features
of this work**



Further expectation

- In summary, an asymmetric total synthesis of sesterterpene natural product (-)-retigeranic acid A in 18 linear steps from commercially available geraniol has been achieved.
- The prominent features of the present synthesis include...
- The current strategy would enable flexible access to other related cyclopentanes with quaternary stereochemical centers embedded in many natural products and their derivatives.

Representative Examples

The **pivotal** Conia-ene reaction went through a *5-exo-dig* cyclization smoothly to give aldehyde **5** in 88% yield. (关键的; key, crucial...)

Regardless of the catalysts employed, **exhaustive** attempts to achieve the crucial C-2 stereochemical inversion proved fruitless. (详尽的; detailed)

Hydrogenation of the C1-C2 double bond of diene **18** with Adam, Wilkinson, or Crabtree catalyst were **thwarted**. (失败的; unsuccessful, failed)

***Thanks
for your attention***