Literature Report I

Concise Total Syntheses of (−)-Crinipellins A and B Enabled by a Controlled Cargill Rearrangement

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Checker: Yu-Qing Bai

Xu, B.; Zhang, Z.; Tantillo, D. J.; Dai, M. *J. Am. Chem. Soc.* **2024**, *146*, 21250

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CV of Prof. Mingji Dai

Background:

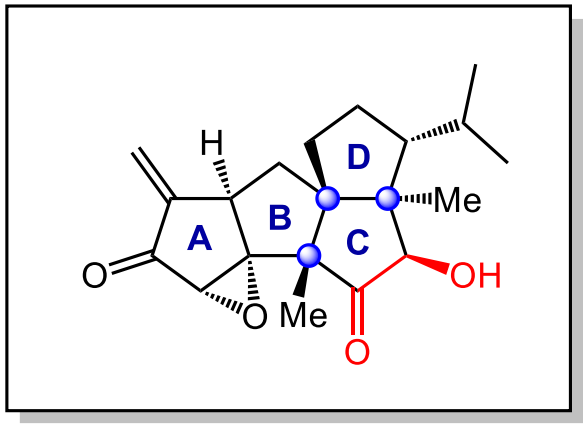
- **1998-2002** B.S., Peking University
- **2002-2004** Research Assistant, Peking University
- **2004-2009** Ph.D., Columbia University
- **2009-2012** Postdoctoral Fellow, Harvard University
- **2012-2020** Assistant Professor, Associate Professor, Purdue University
- **2020-2022** Professor, Purdue University
- **2022-Now** Professor, Emory University

Research Field:

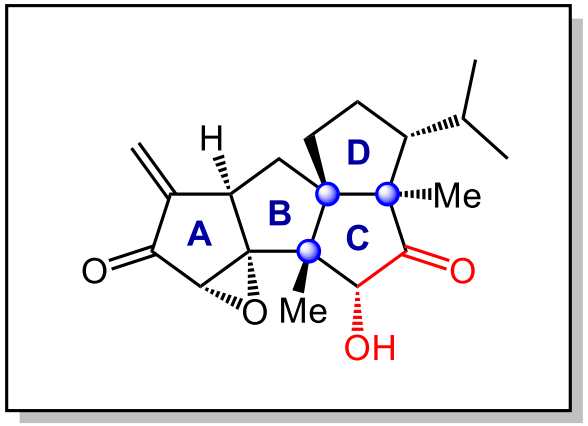
- Total Syntheses of Natural and Unnatural Molecules
- Synthetic Methodology

Contents

Introduction



(−)-Crinipellin A



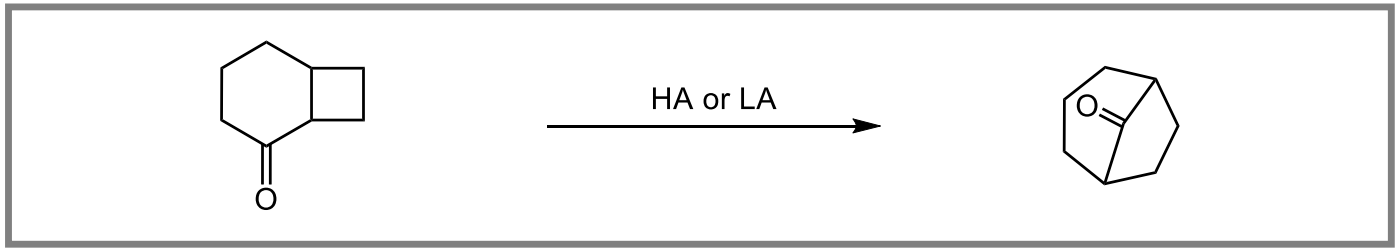
(−)-Crinipellin B

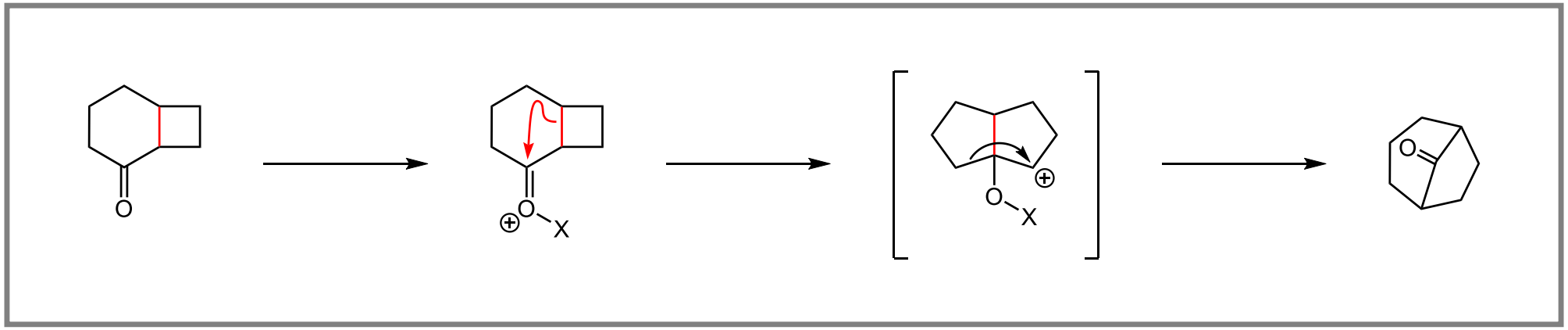
Crinipellis Stipitaria

- They were Isolated from Fungus *Crinipellis Stipitaria* in 1985;
- They Contain a Unique Tetraquinane Skeleton with Three Adjacent All-carbon Quaternary Centers, and Multiple Oxygenated and Labile Functional Groups;
- They Demonstrate a Broad Spectrum of Activities Including Antibacterial and Anticancer.

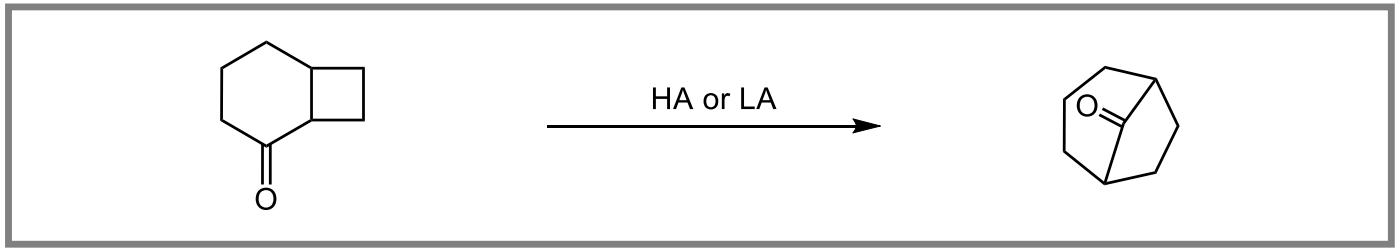
Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W.* *Angew. Chem. Int. Ed.* **1985**, *24*, 709

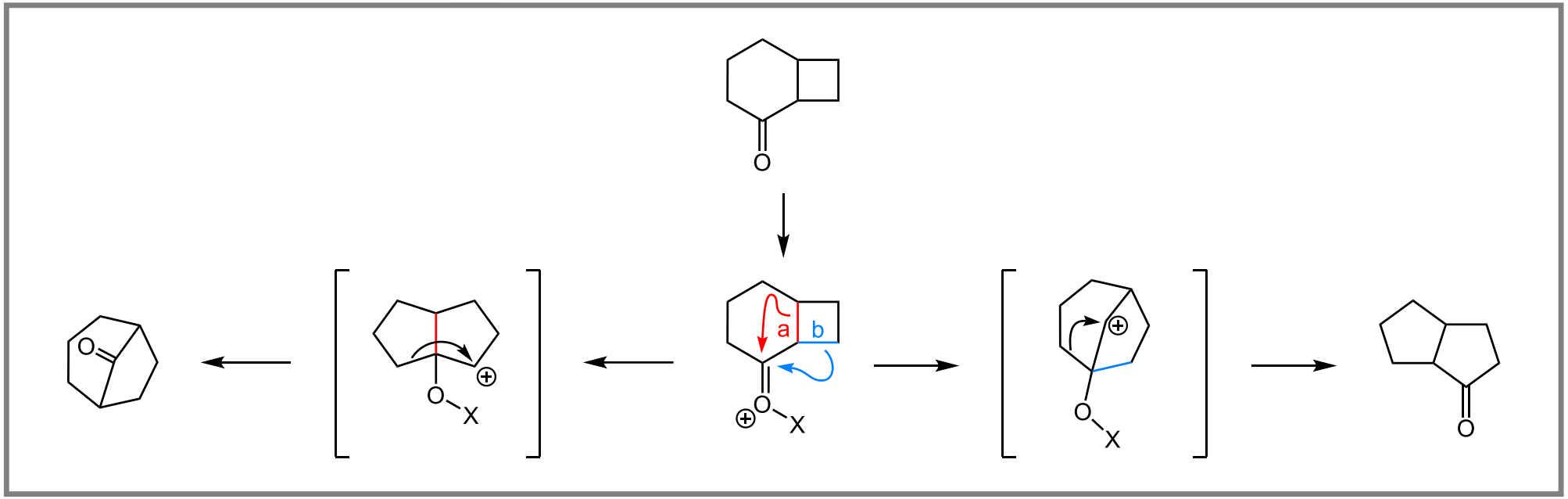
Cargill Rearrangement



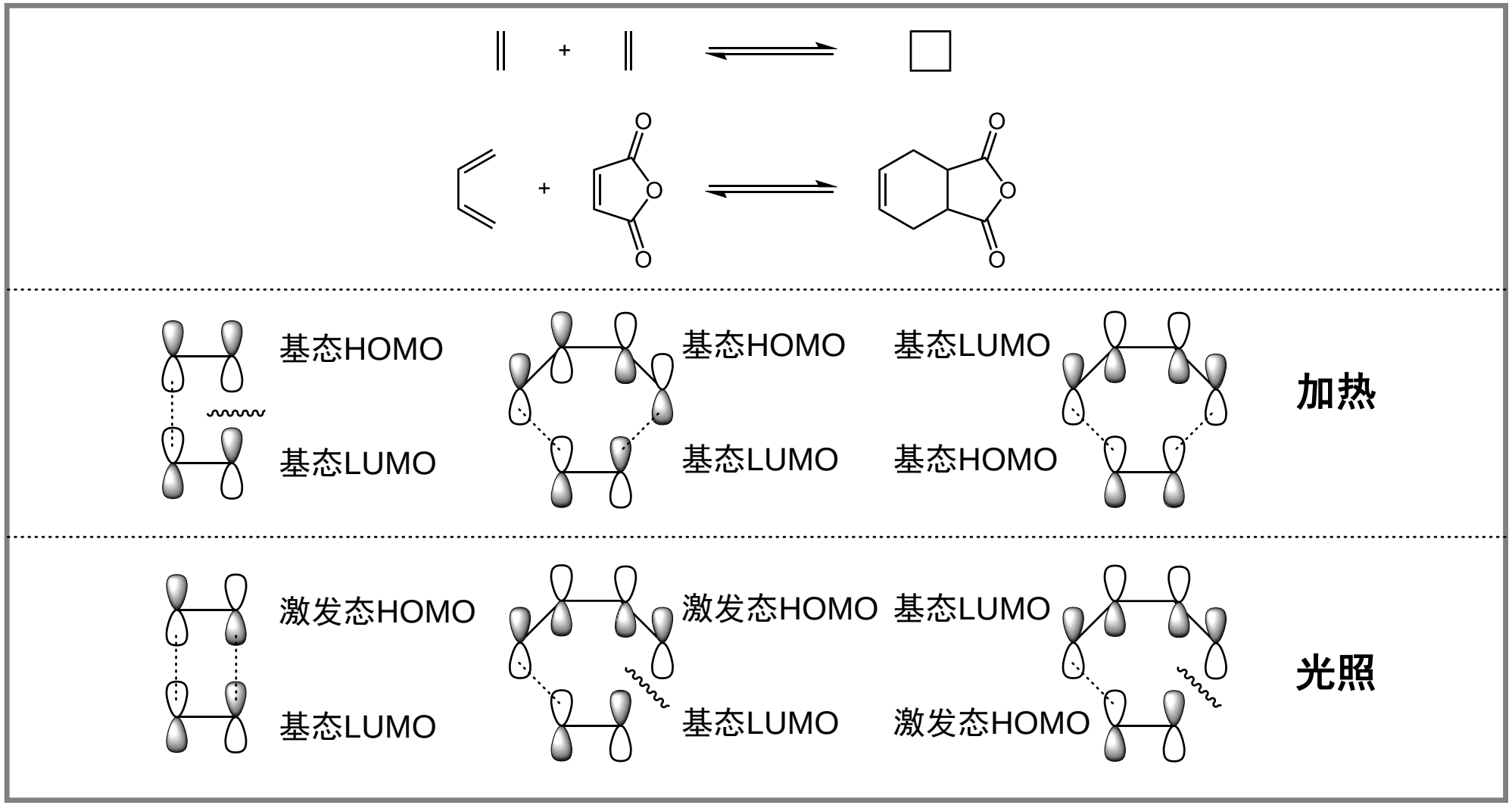


Cargill Rearrangement

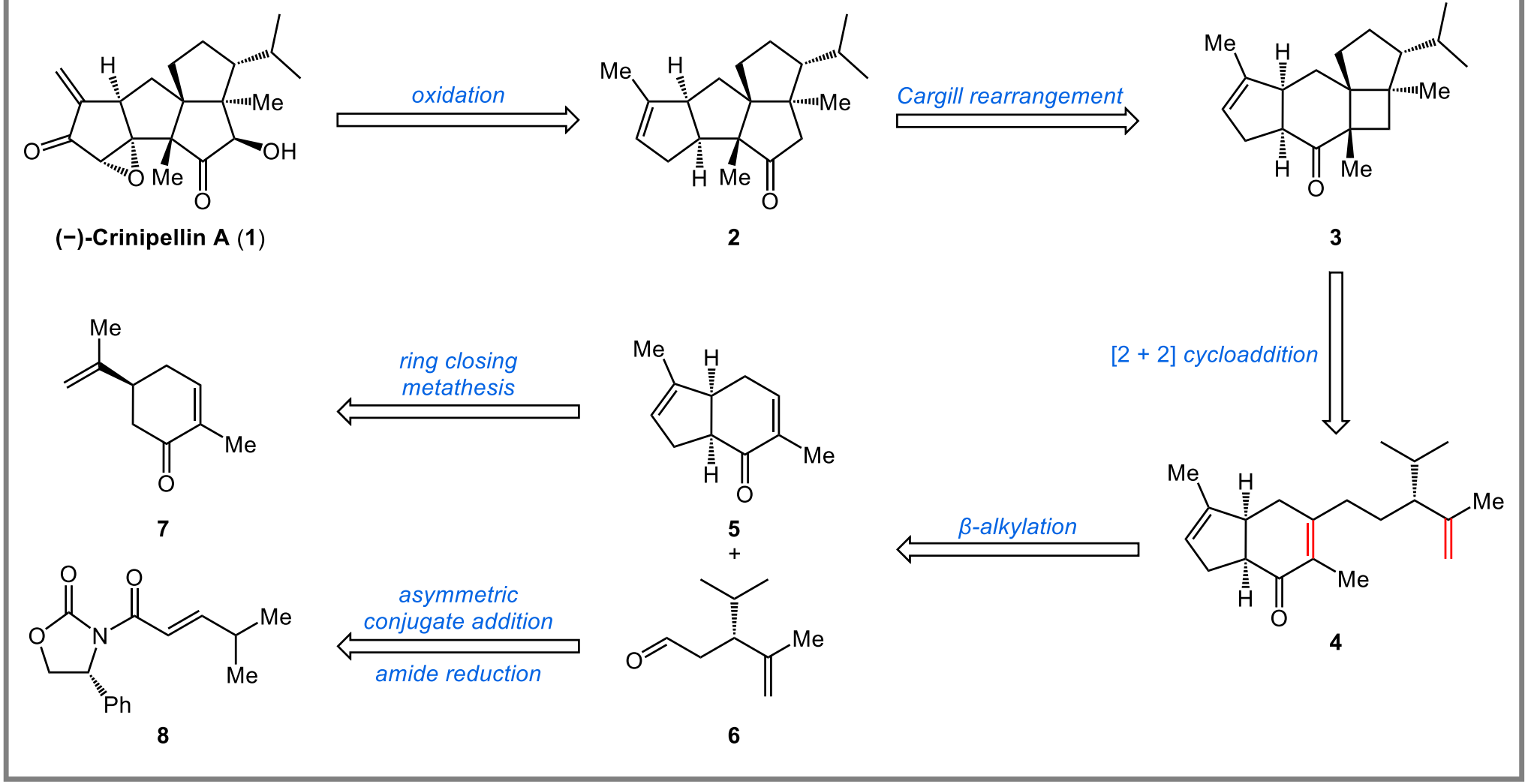




Cycloaddition



Retrosynthetic Analysis



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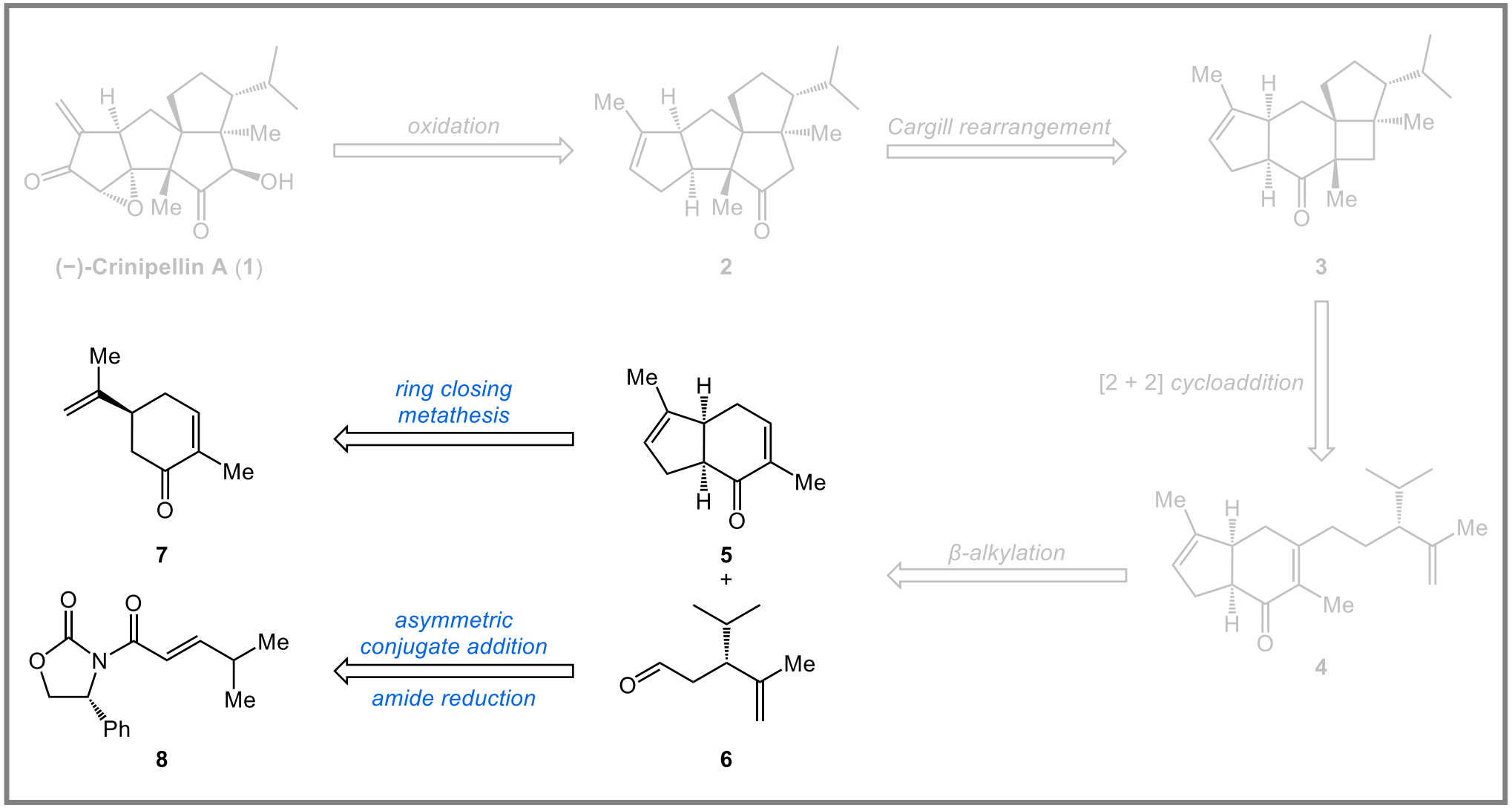
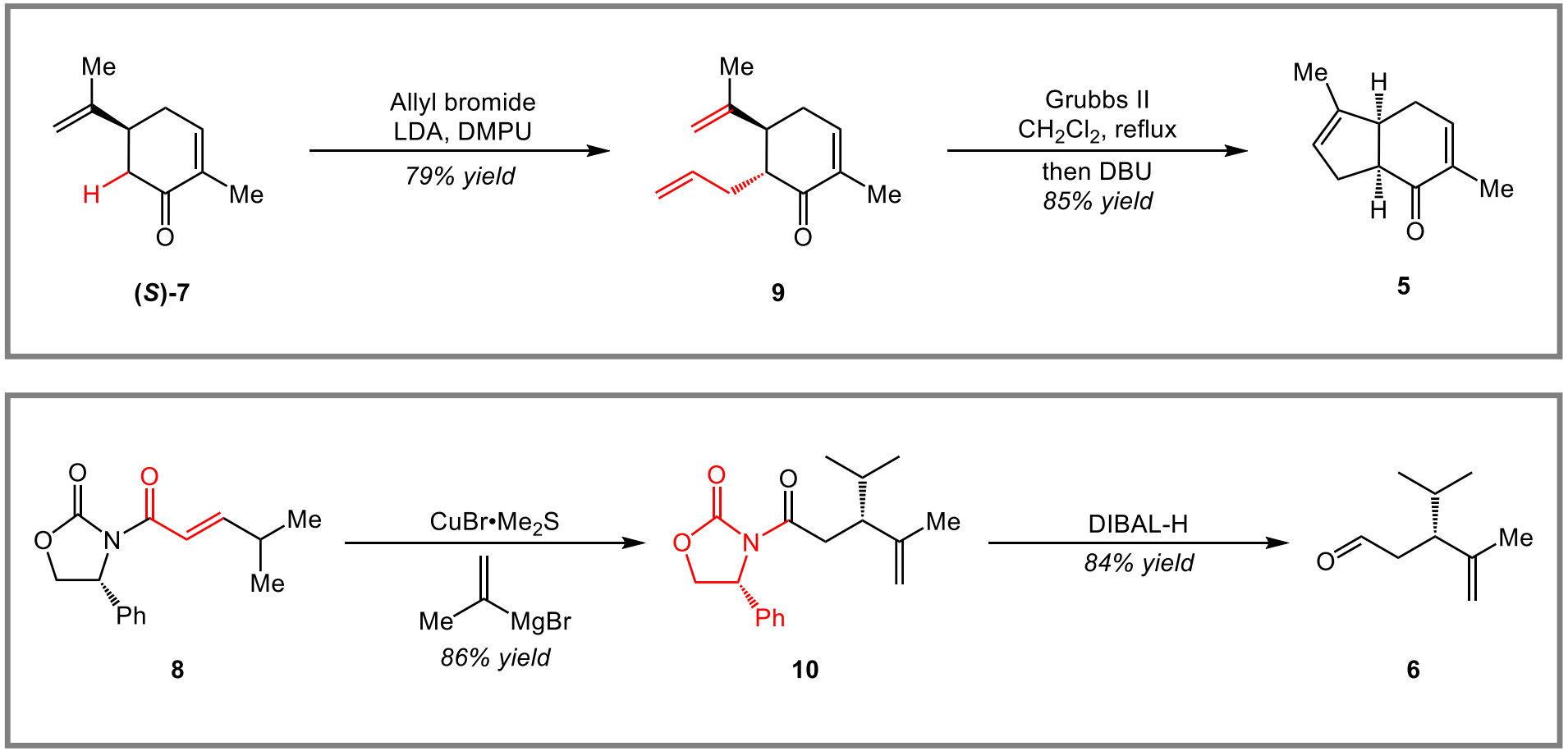
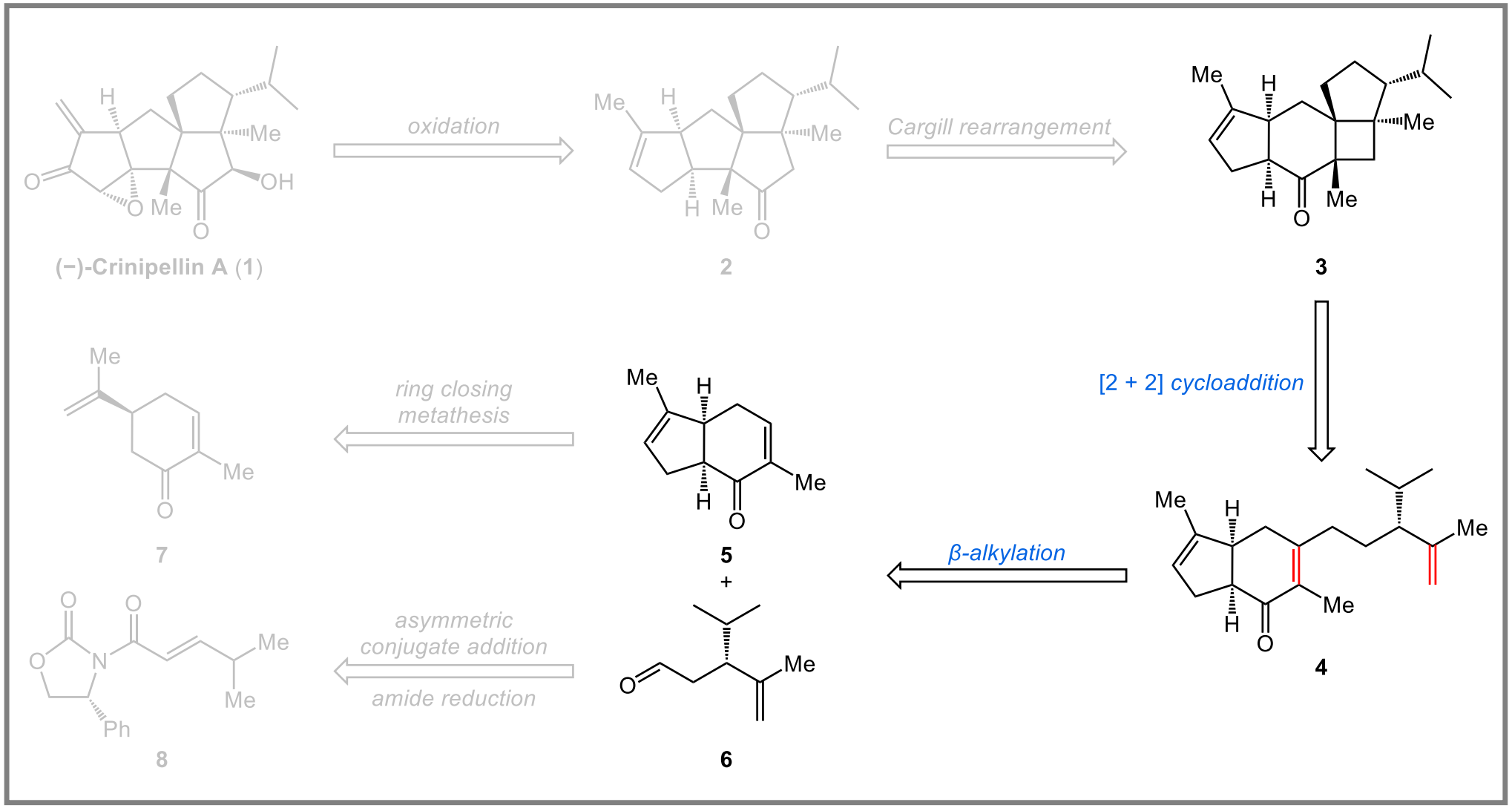


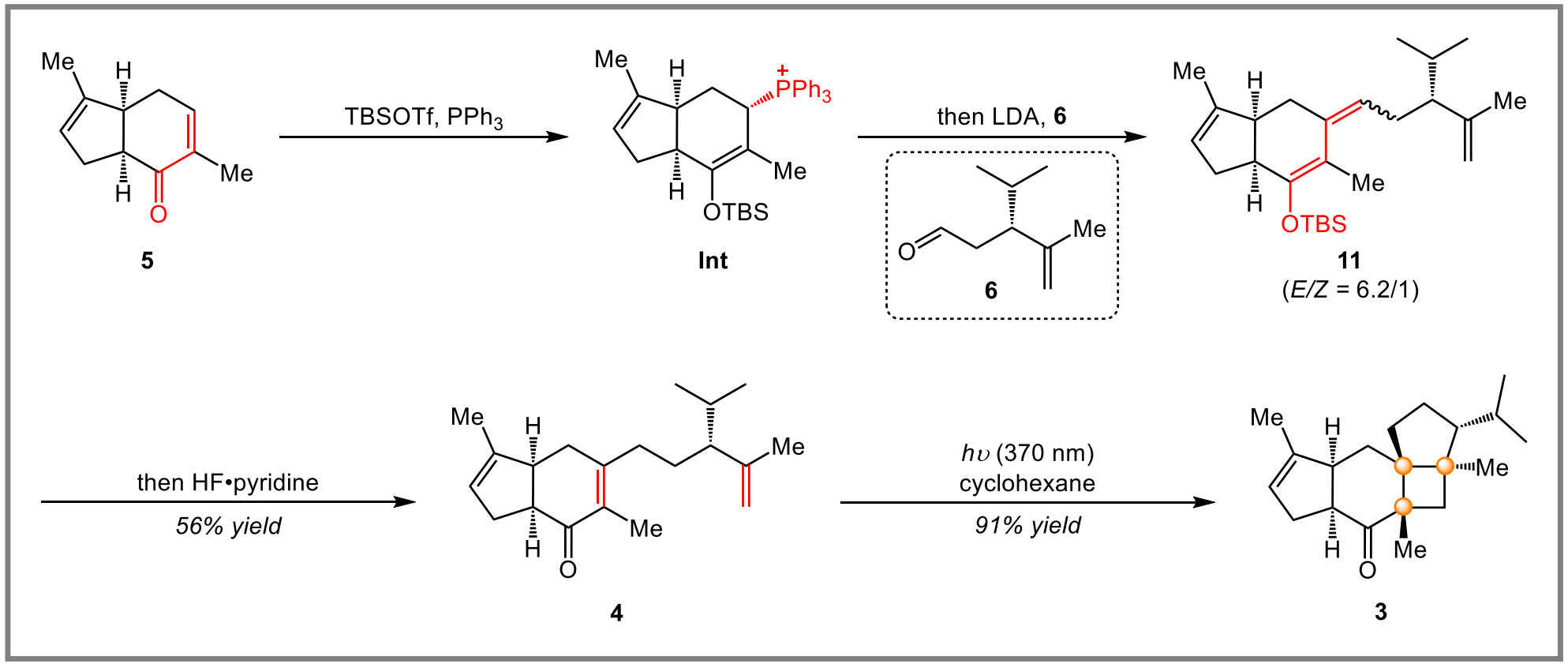
Syntheses of Compounds 5 and 6



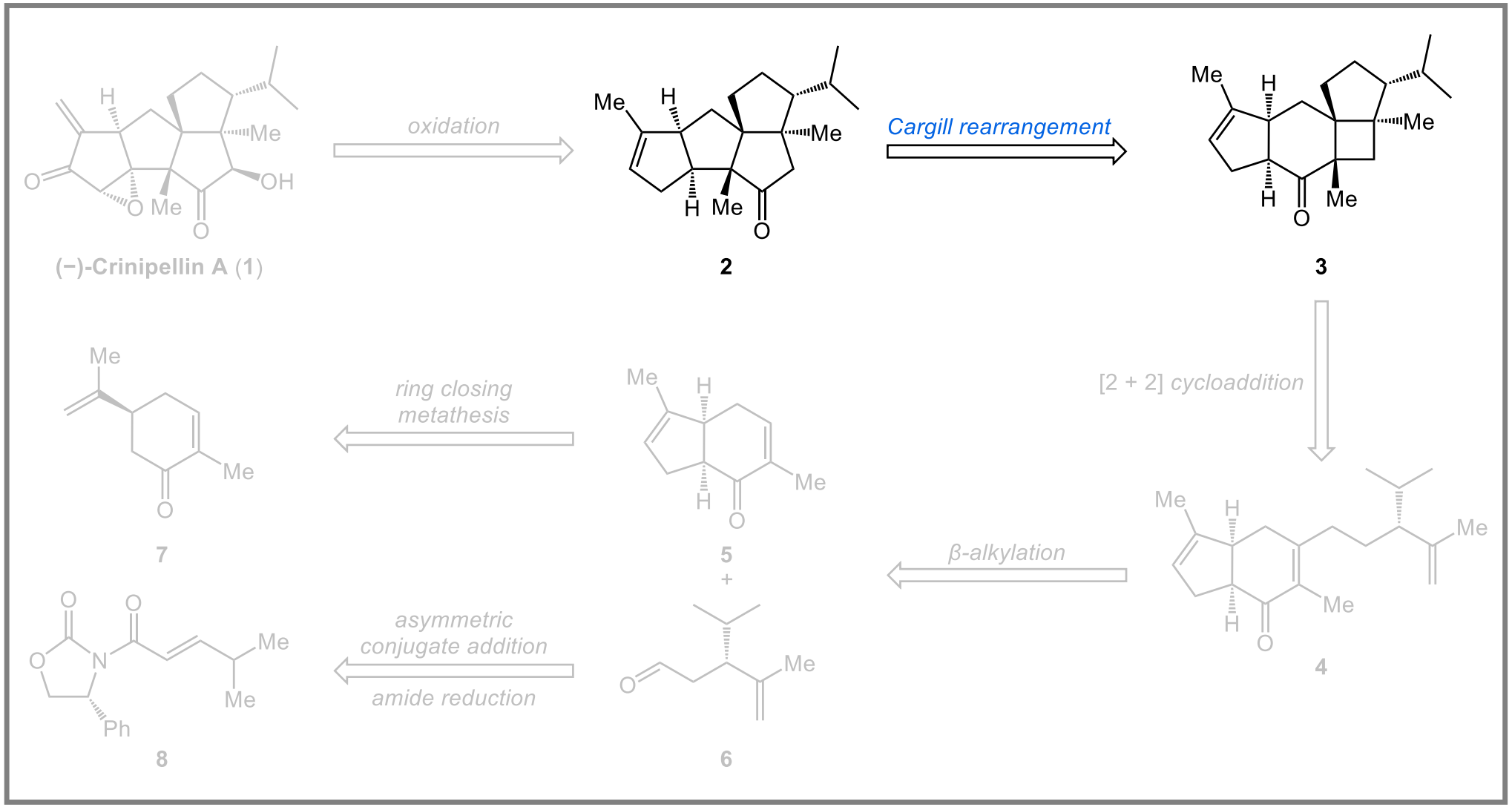
Retrosynthetic Analysis



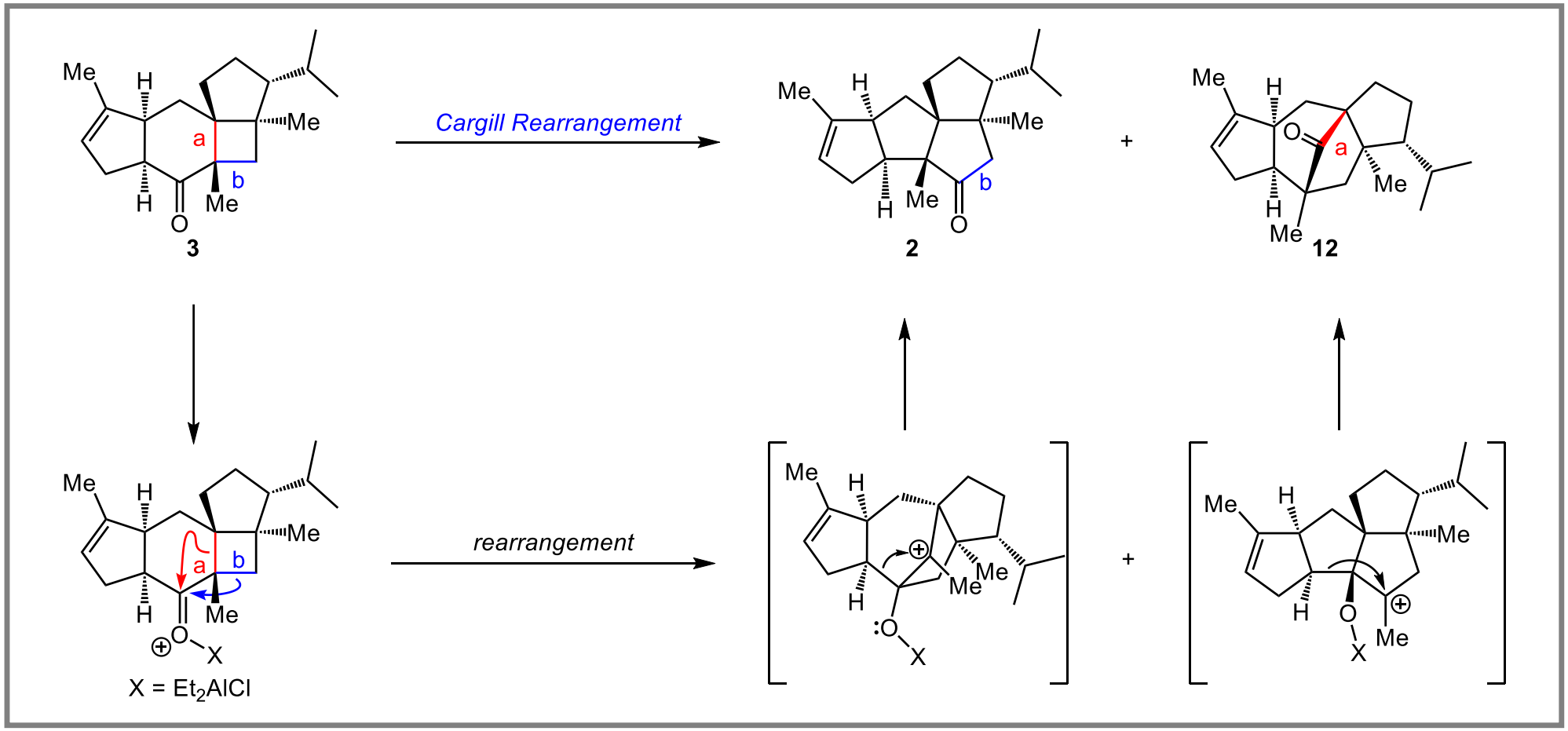
Synthesis of Compound 3



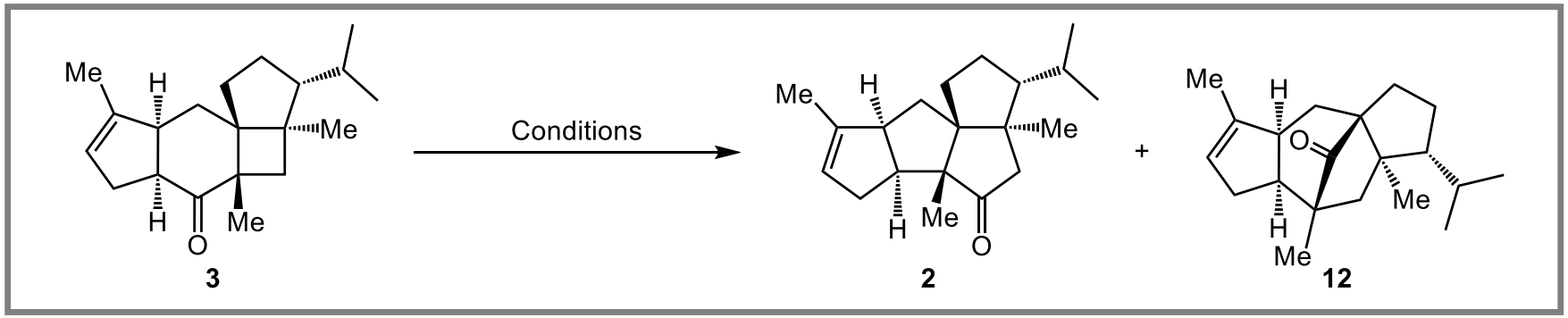
Retrosynthetic Analysis



Synthesis of Compound 2

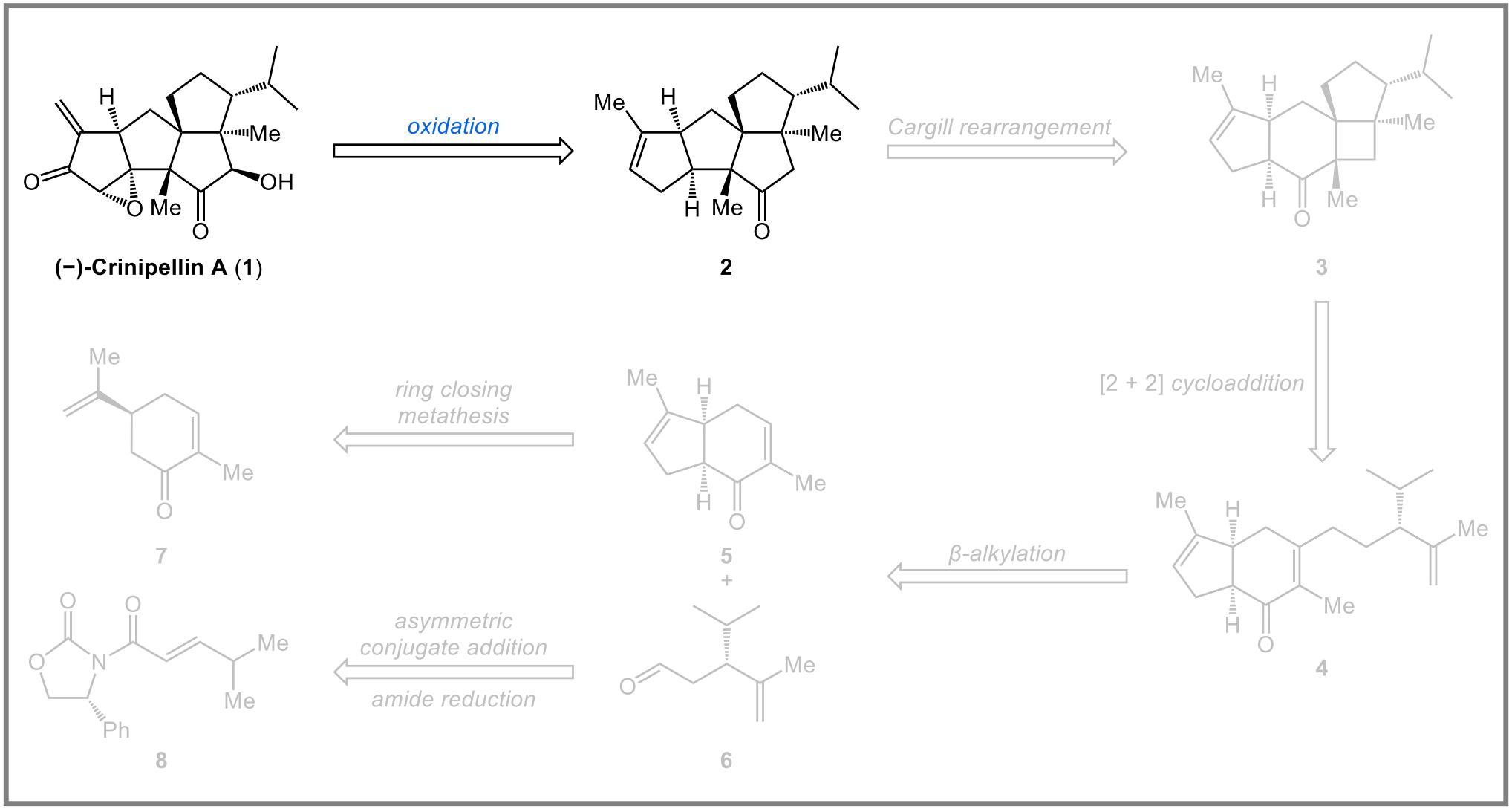


Optimization of Cargill Rearrangement

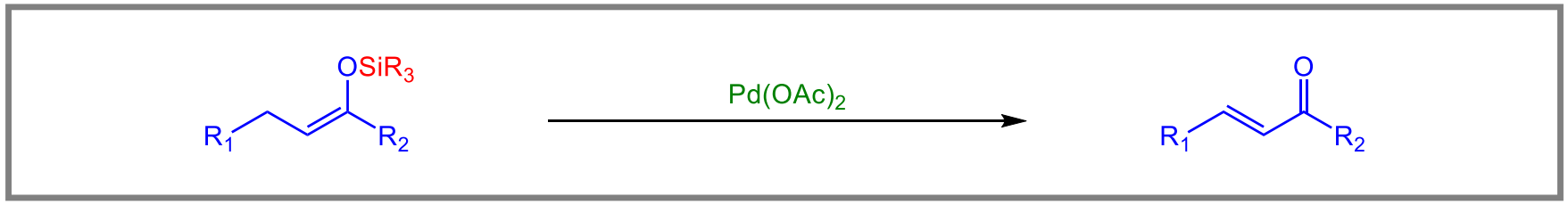


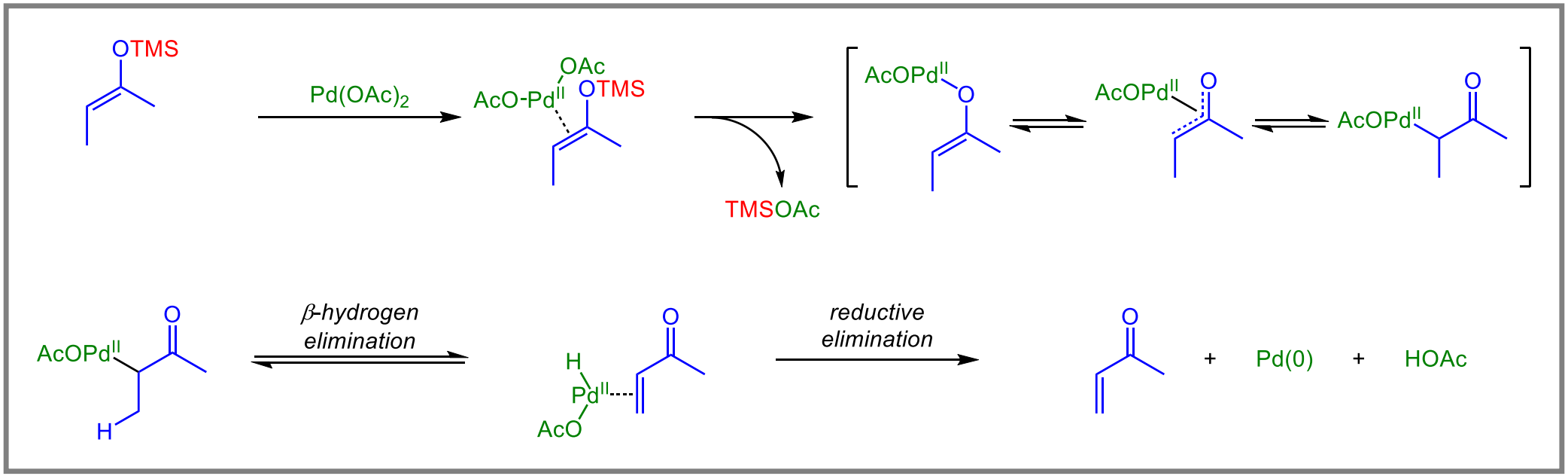
Entry	Conditions	Yield of 2 (%)	Yield of 12 (%)
1	*p*-TsOH, PhH, 80 °C	18	45
2	*p*-TsOH, LiCl, Toluene, 23 °C	0	0
3	Tf_2NH, DCM, 23 °C	9	51
4	$Mg(ClO_4)_2$, CH_2Cl_2, 23 °C	0	0
5	$AlCl_3$, CH_2Cl_2, 23 °C	5	42
6	Me_2AlCl, CH_2Cl_2, 23 °C	32	45
7	Et_2AlCl, CH_2Cl_2, 23 °C	35	23
8	**Et_2AlCl, Toluene, 23 °C**	**65**	**16**
9	Et_2AlCl, LiCl, Toluene, 23 °C	59	9
10	**Et_2AlCl, Toluene, 18 °C (Gram Scale)**	**54**	**9**

Retrosynthetic Analysis

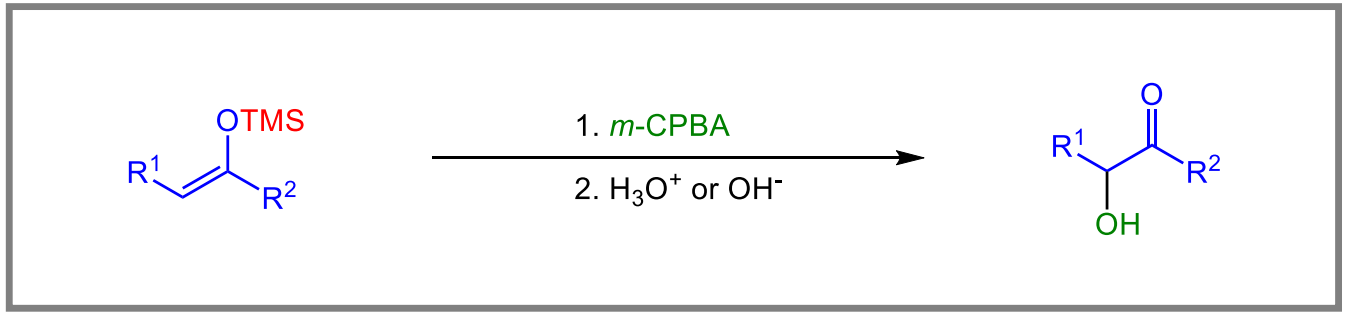


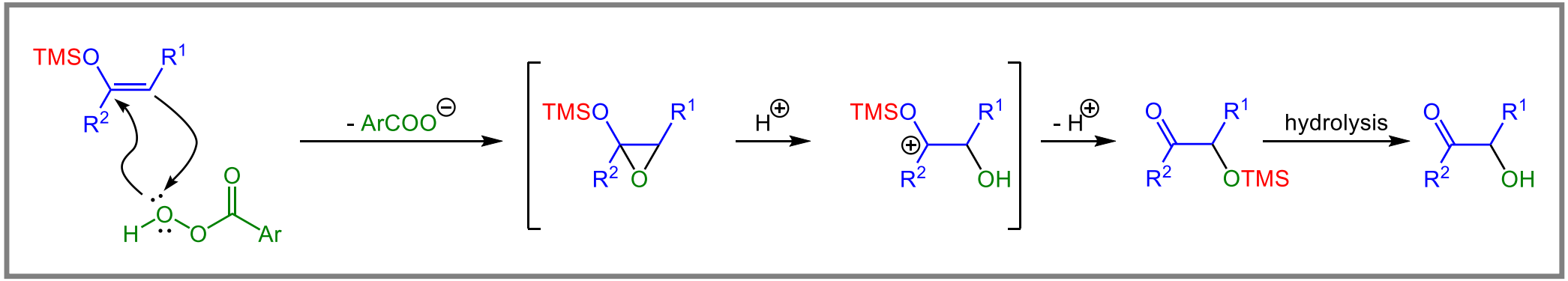
Saegusa-Ito Oxidation



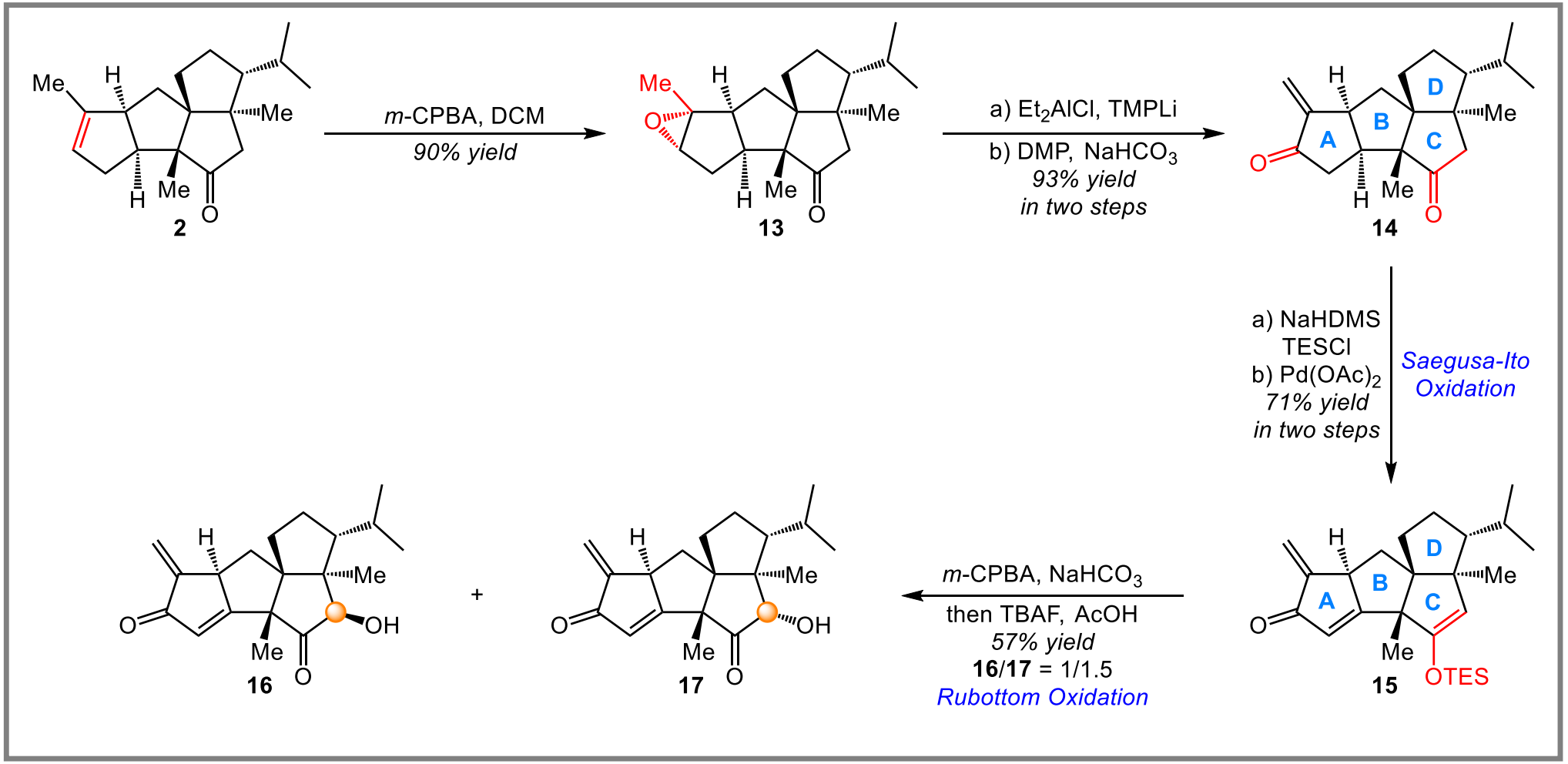


Rubottom Oxidation

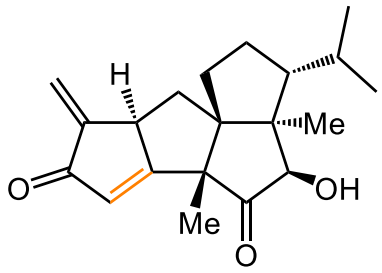




Syntheses of Compounds 16 and 17



Syntheses of (−)-Crinipellins A and B



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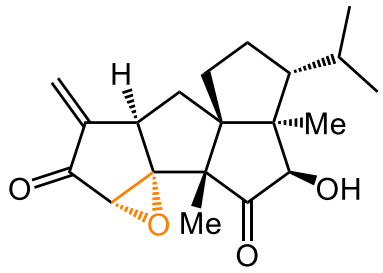
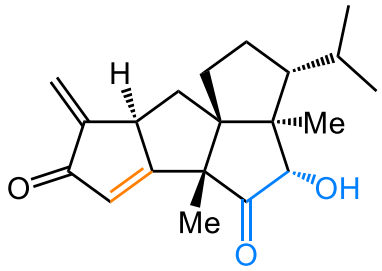


(−)-Crinipellin A



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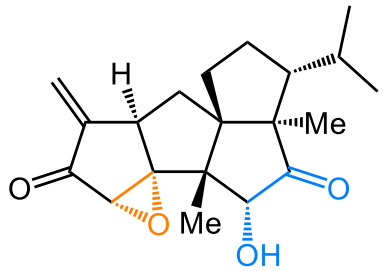
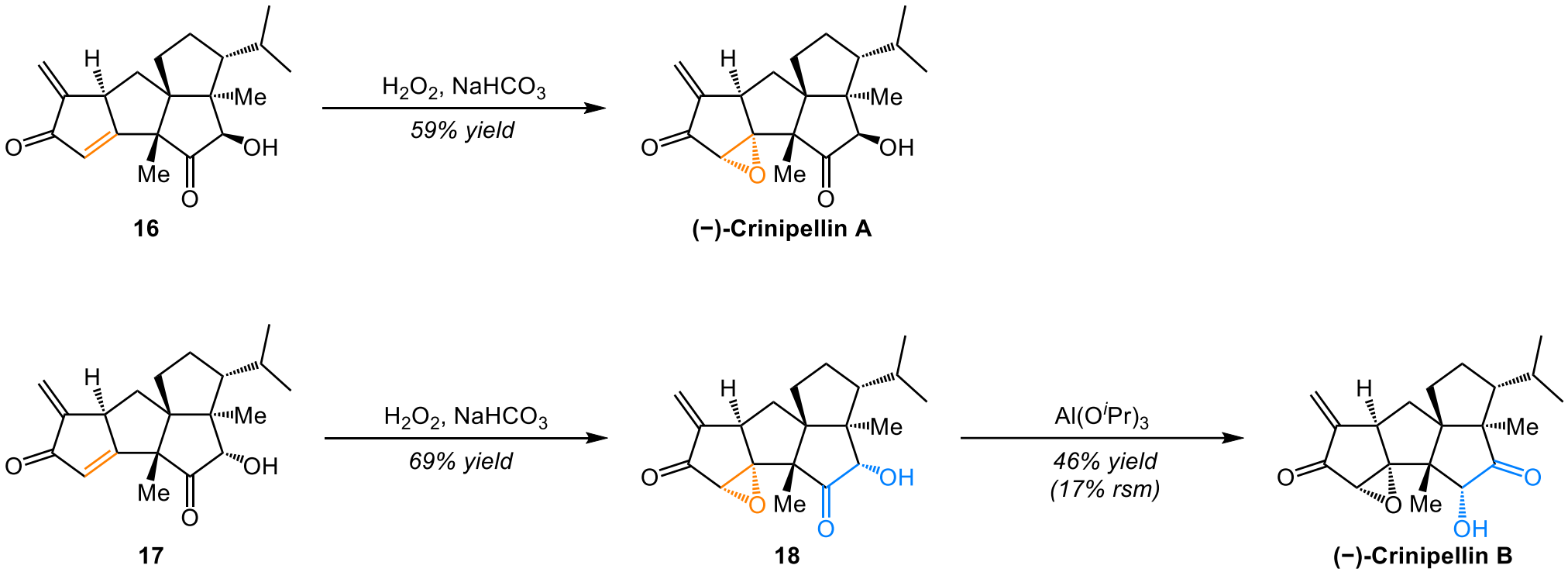
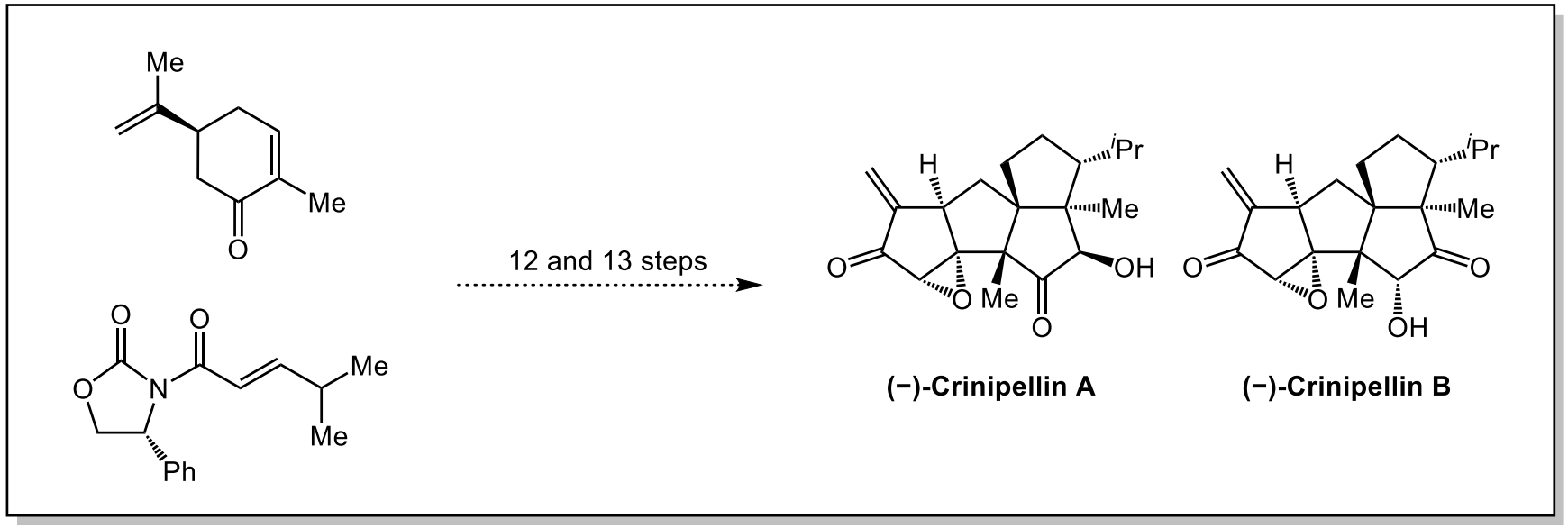


(−)-Crinipellin B

Syntheses of (−)-Crinipellins A and B



Summary



- Intramolecular [2+2] Cycloaddition;
- Controlled Cargill Rearrangement (Tetraquinane Skeleton);
- Three Adjacent All-carbon Quaternary Centers.

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Writing Strategy

➢ **First Paragraph**

Structure and History

Biological Activity

Retrosynthetic Analysis

- Crinipellins A, B, and related natural congeners belong to the polyquinane diterpene natural products. Crinipellins A and B were isolated by Steglich from *Crinipellis Stipitaria*. Since then, many other Crinipellins were discovered.
- Biologically, Crinipellins A and B have demonstrated broad spectrum of activities including antibacterial, anticancer, and fibrinolytic activities.
- Retrosynthetically, **33** was proposed as an advanced intermediate, which could be further oxidized to Crinipellins. We envisioned that **33** with the tetraquinane core could be derived from **34** with 5/6/4/5 tetracyclic skeleton.

Writing Strategy

Last Paragraph

Summary

Key Steps

Prospect

- In summary, starting from the cheap and abundant chiral molecule (*S*)-carvone, we completed total syntheses of (−)-Crinipellins A and B in 12 and 13 steps, respectively.
- The key steps include an intramolecular photochemical [2+2] cycloaddition to install three challenging and adjacent all-carbon quaternary centers and a 5/6/4/5 tetracyclic skeleton, and a Cargill rearrangement to convert the 5/6/4/5 tetracyclic skeleton to desired tetraquinane skeleton.
- Notably, a set of conditions were developed to get either bridged or fused product *via* the Cargill rearrangement. DFT studies indicated that both stepwise and concerted mechanisms are possible for these rearrangements.

Representative Examples

- The Brønsted acid-catalyzed Cargill rearrangements likely involve stepwise paths to products and the AlR_3-catalyzed Cargill rearrangements likely involve a concerted path with asynchronous alkyl shifting events to form the desired product. (*adj*. 不同时的, 不同期的; 反义词：synchronous，同时的，同期的)

- Biologically, Crinipellins A and B have demonstrated a broad spectrum of activities including anti-bacterial, anticancer, and fibrinolytic activities. (广泛的)

- The *α*-methylene ketone and *α*,*β*-epoxide moieties of Crinipellins A and B render both of them potential protein covalent modifiers. (*v*. 使成为, 使处于某种状态)

Acknowledgement

Thank You for Your Attention!

18 to Crinipellin B