Literature Report 1

Enantioselective Total Synthesis of Cheloviolene A

Reporter: Zi-Biao Zhao

Checker: Ji Zhou

Date: 2017-11-27

Slutskyy, Y.; Jamison, C. R.; Zhao, P.; Lee, J.; Rhee, Y. H.; **Overman, L. E.***
J. Am. Chem. Soc. **2017**, *139,* 7192-7195.

CV of Prof. Larry E. Overman

Background:

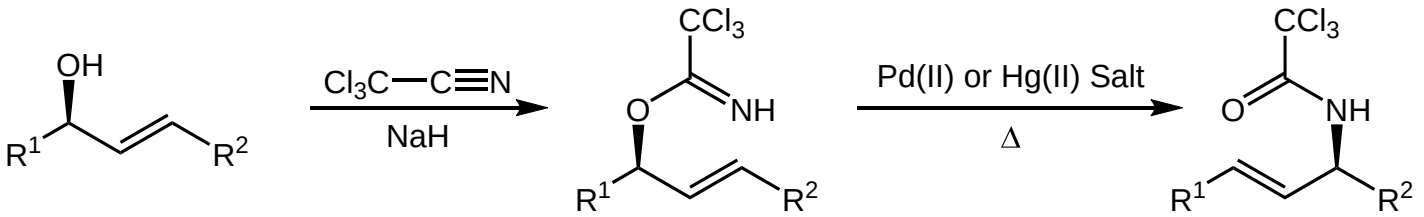
- **1965** B.Sc., Earlham College
- **1969** Ph.D., Chemistry, University of Wisconsin
- **1970** Postdoctoral Fellow, Advisor: Prof. Breslow
- **1971** University of California, Irvine

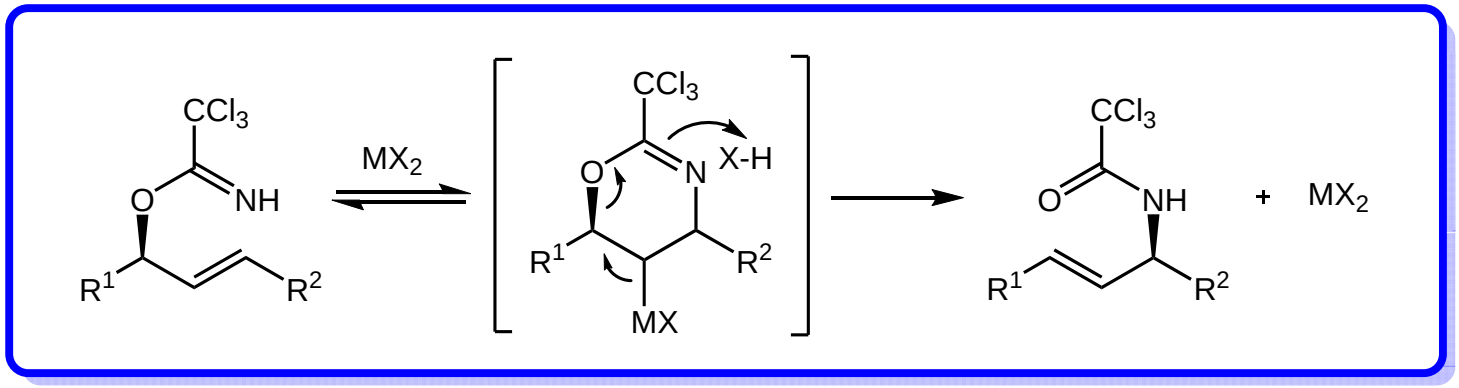
  (Full Professor in 1979)

Research:

- Invention of new reactions and strategies in organic synthesis.
- Total synthesis of natural products and their congeners.
- Total synthesis of agents displaying a variety of pharmacological activities.

Overman Rearrangement





Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96,* 597

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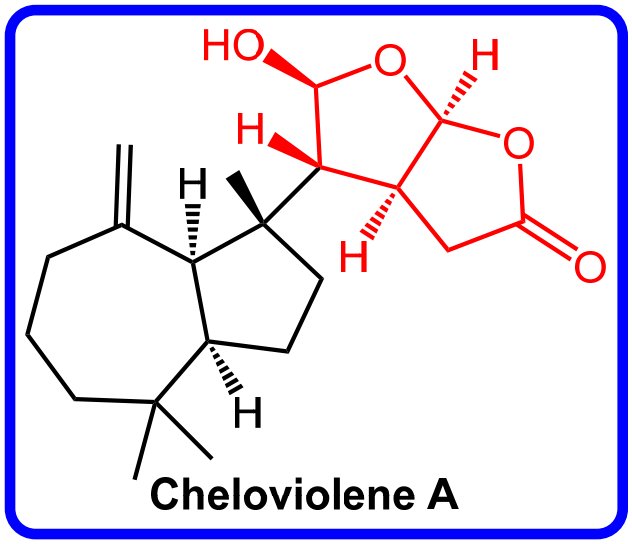
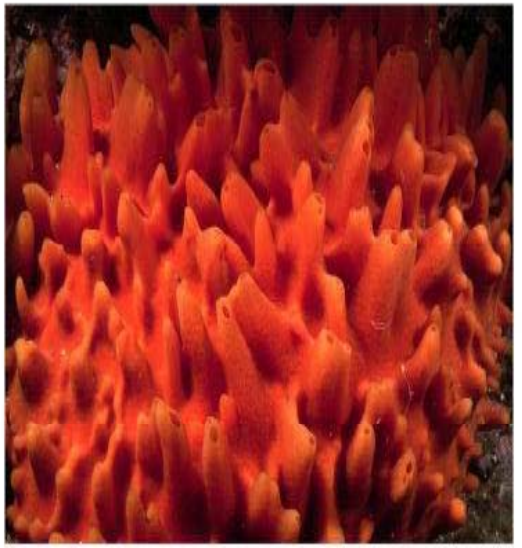
Introduction



Cheloviolene A

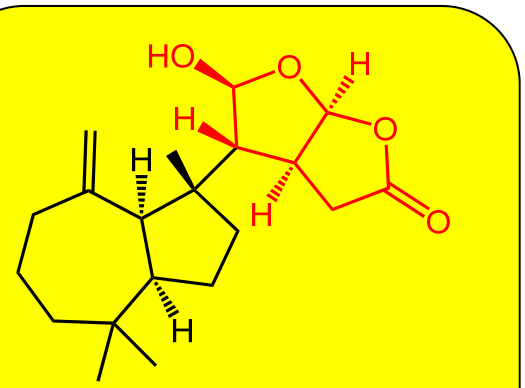


Marine sponges

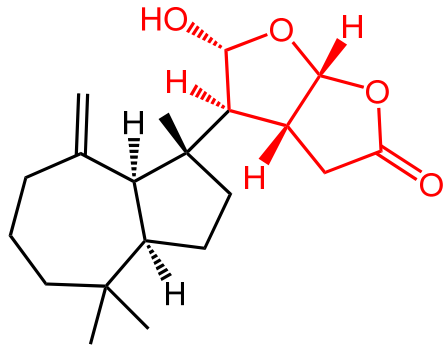
- It was isolated from Marine sponges or nudibranchs;
- It belongs to a family of marine diterpenes;
- It could block protein transport from the Golgi to the plasma membrane.

Keyzers, R. A.; Northcote, P. T.; Davies-Coleman, M. T. *Nat. Prod. Rep*. **2006**, *23*, 321

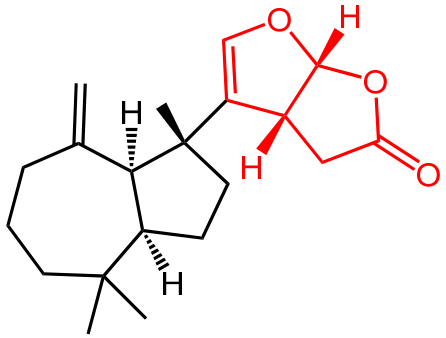
Introduction



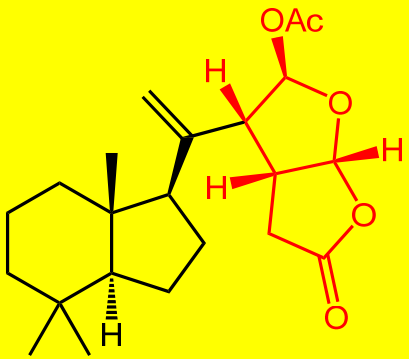
Cheloviolene A



Cheloviolene B

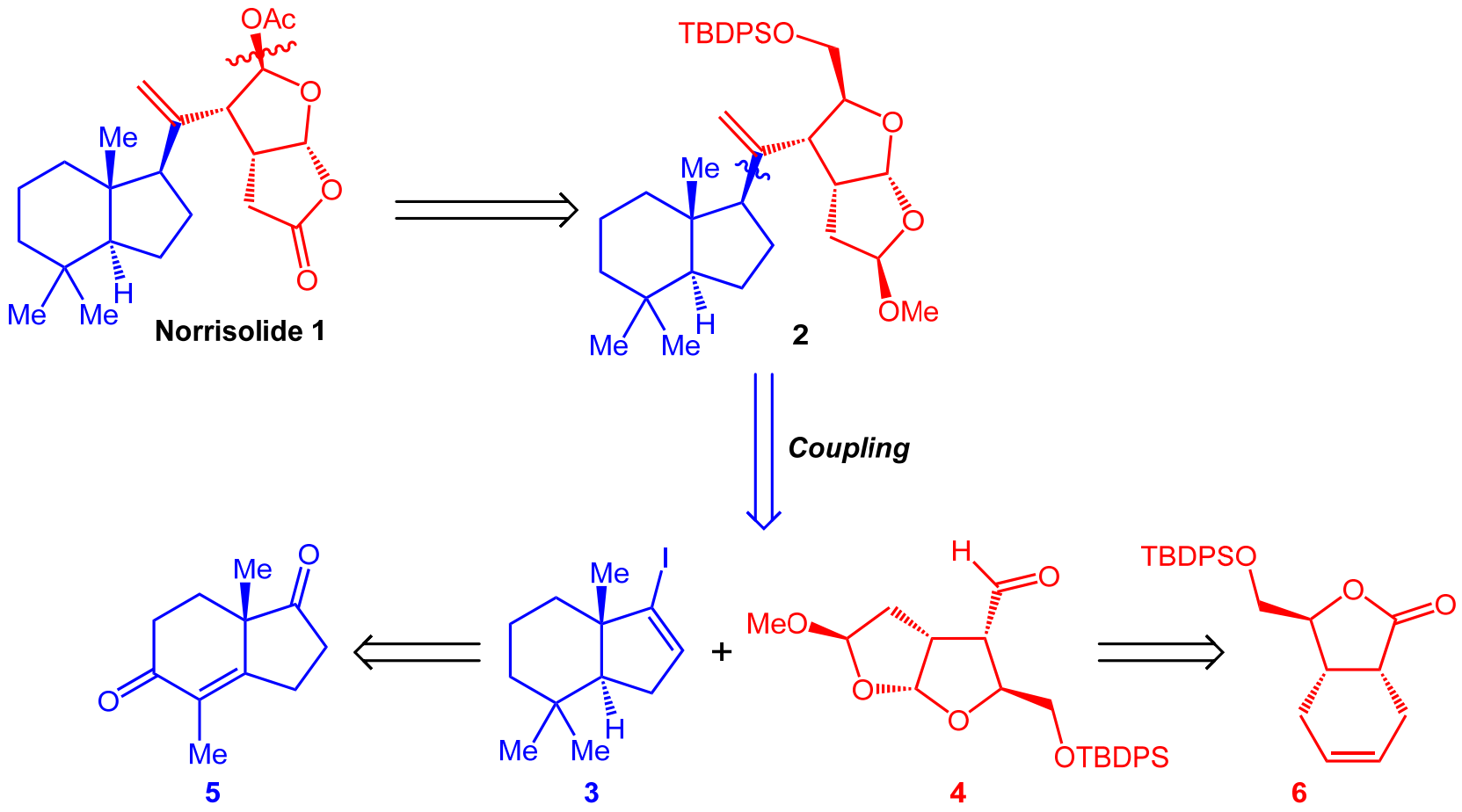


Dendrillolide C



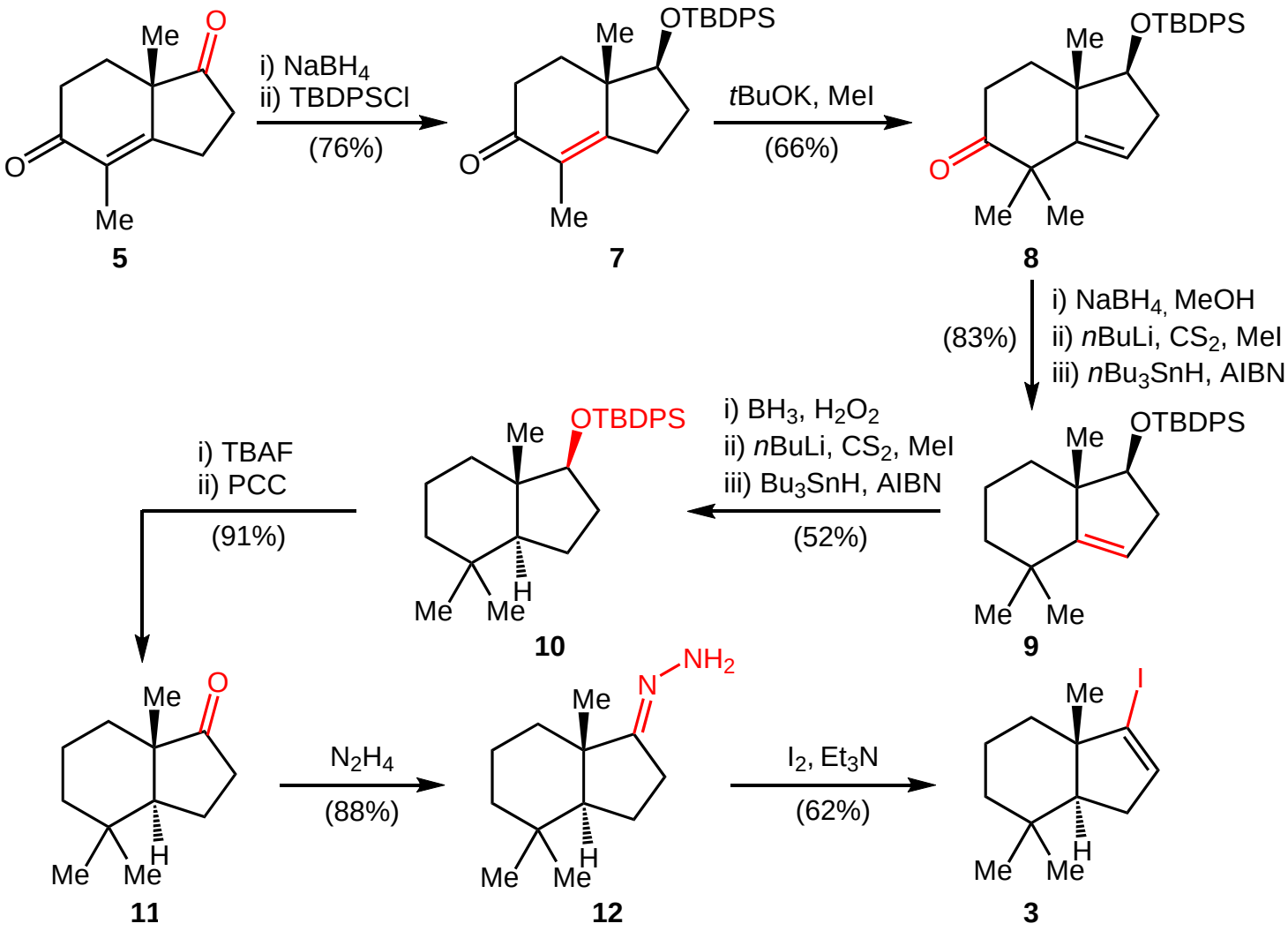
Norrisolide

Retrosynthetic Analysis

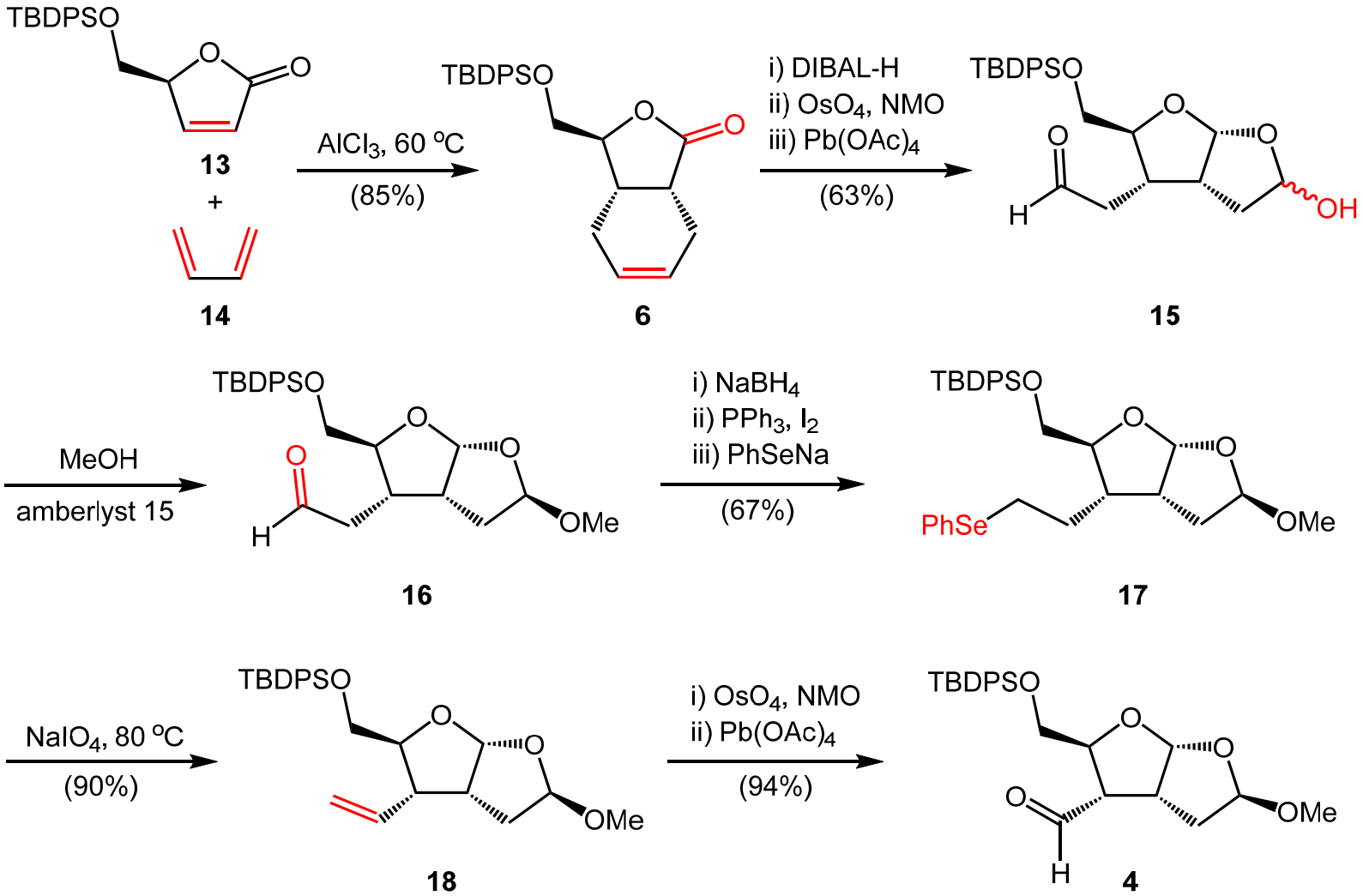


Brady, T. P.; Kim, S. H., Wen, K.; Theodorakis, E. A. *Angew. Chem. Int.* Ed. **2004**, *43*, 739

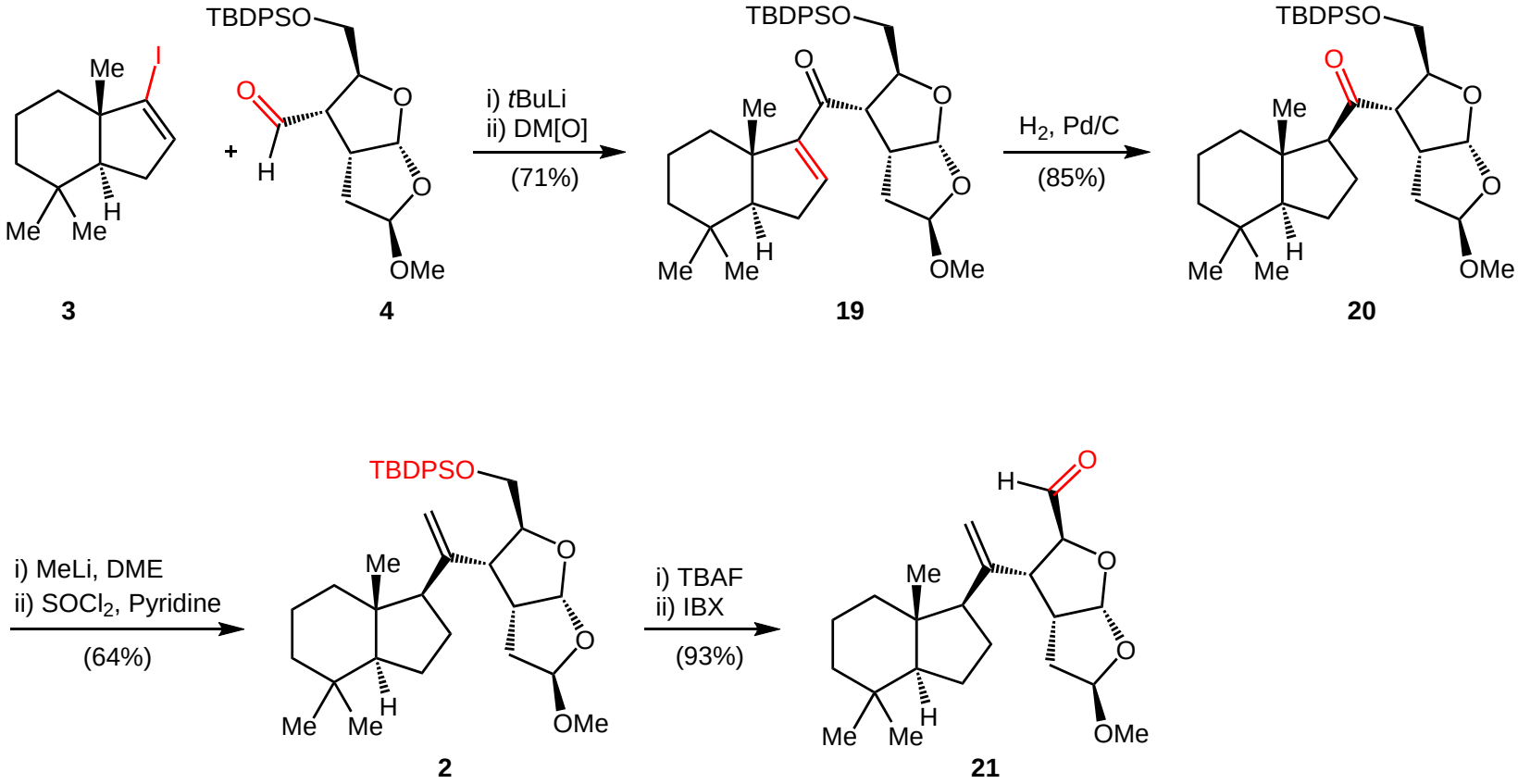
Synthesis of Fragment 3



Synthesis of Fragment 4

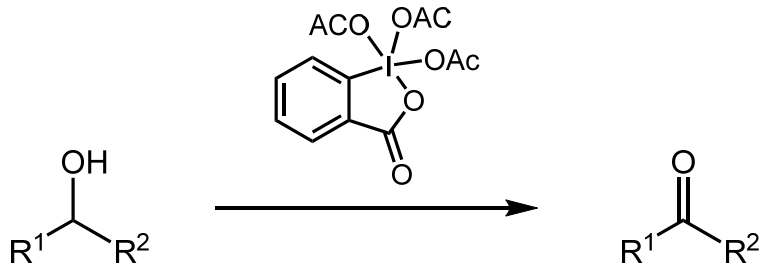


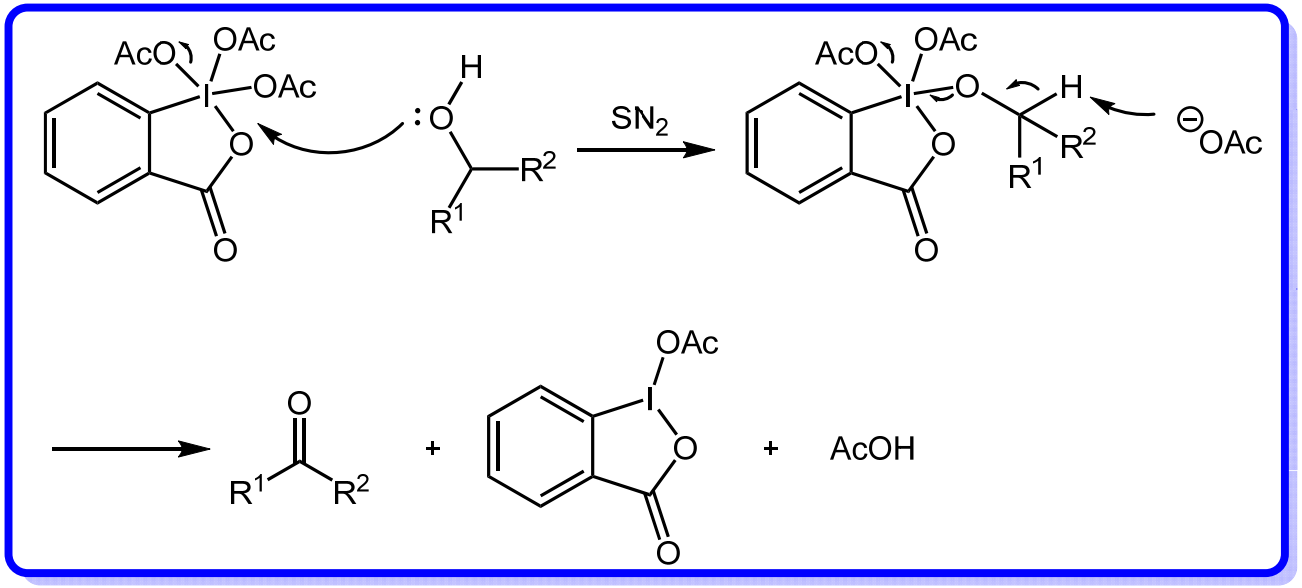
Synthesis of (+)-Norrisolide



3 **4** **19** **20** **2** **21**

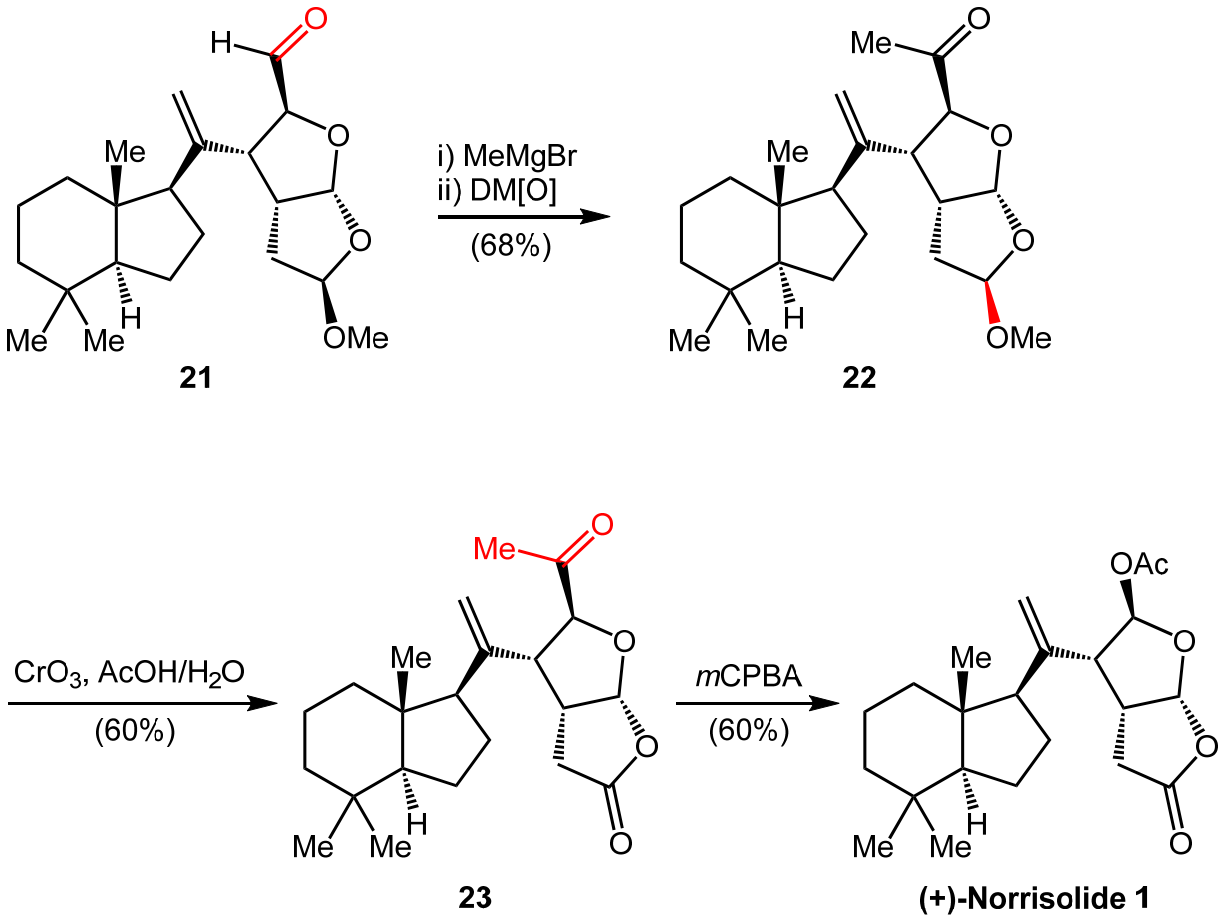
Dess-Martin Periodinane Oxidation



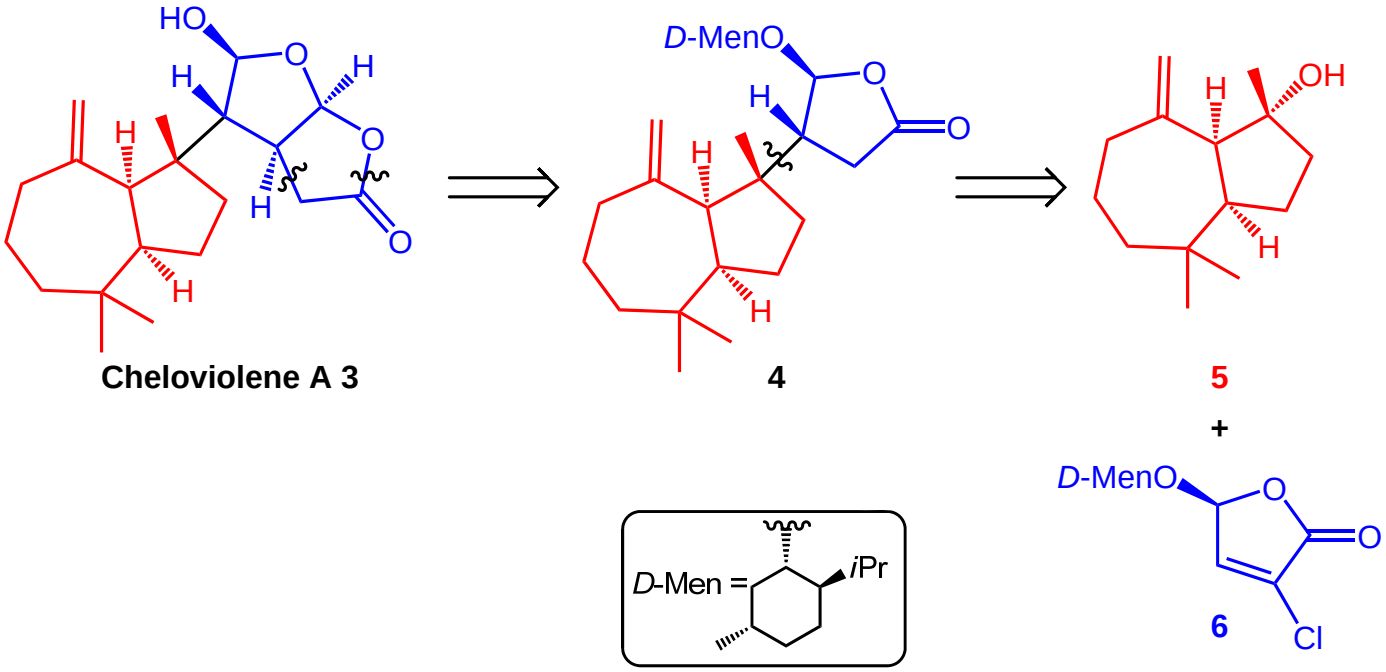


Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155

Synthesis of (+)-Norrisolide

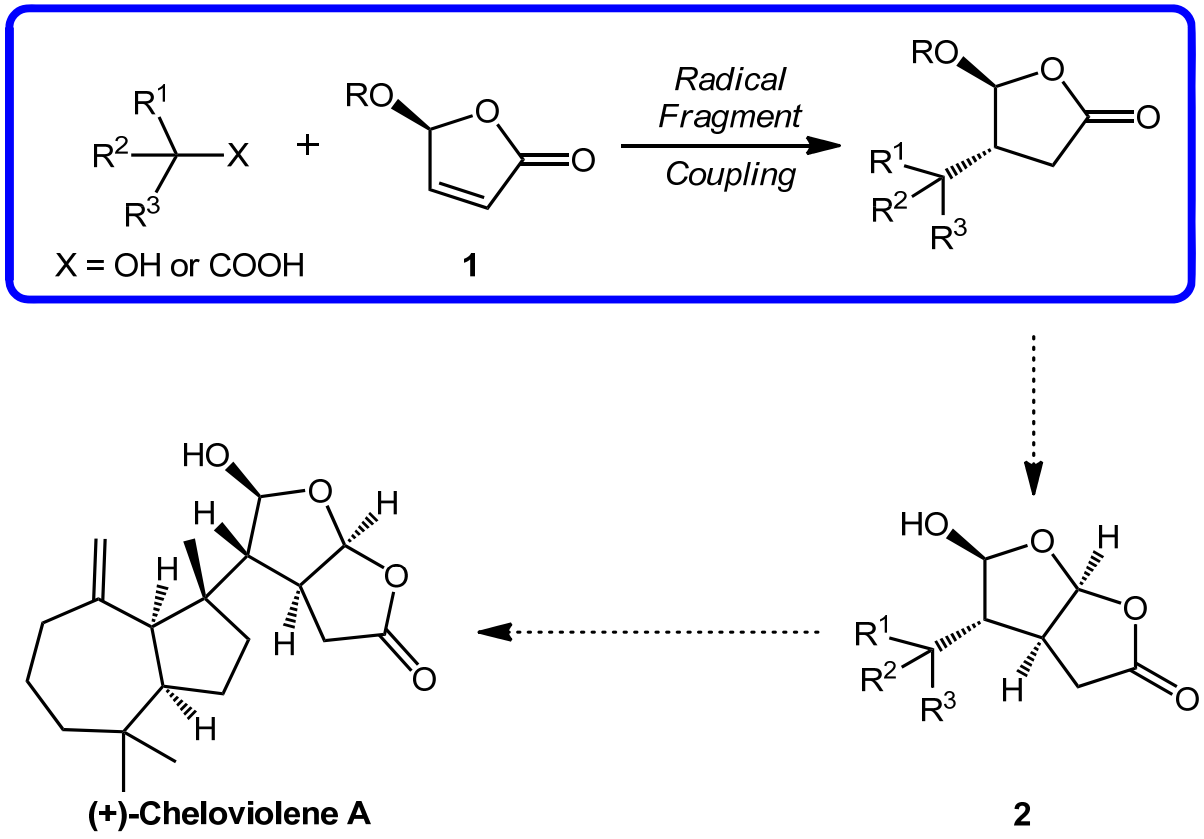


Retrosynthetic Analysis



Slutskyy, Y.; Jamison, C. R.; Zhao, P.; Overman, L. E. *J. Am. Chem*. Soc. **2017**, *139*, 7192

Key Steps of Synthesis of (+)-Cheloviolene A



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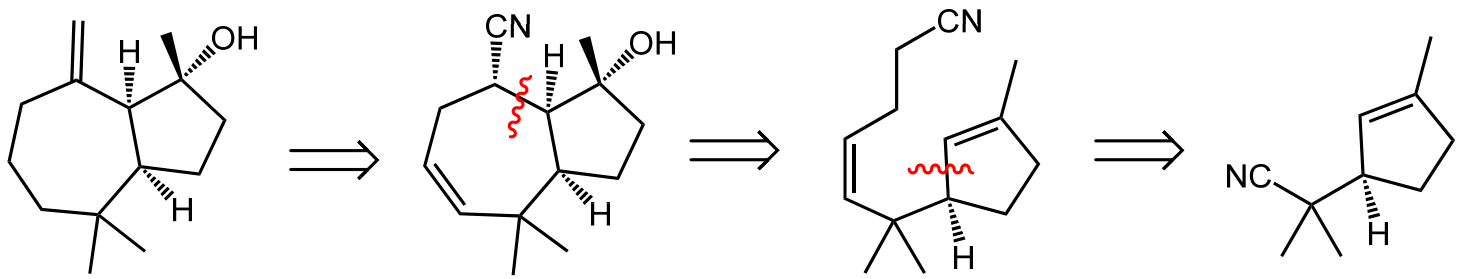
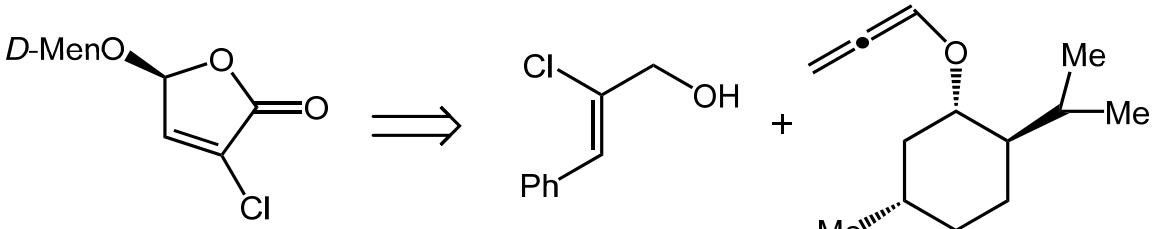
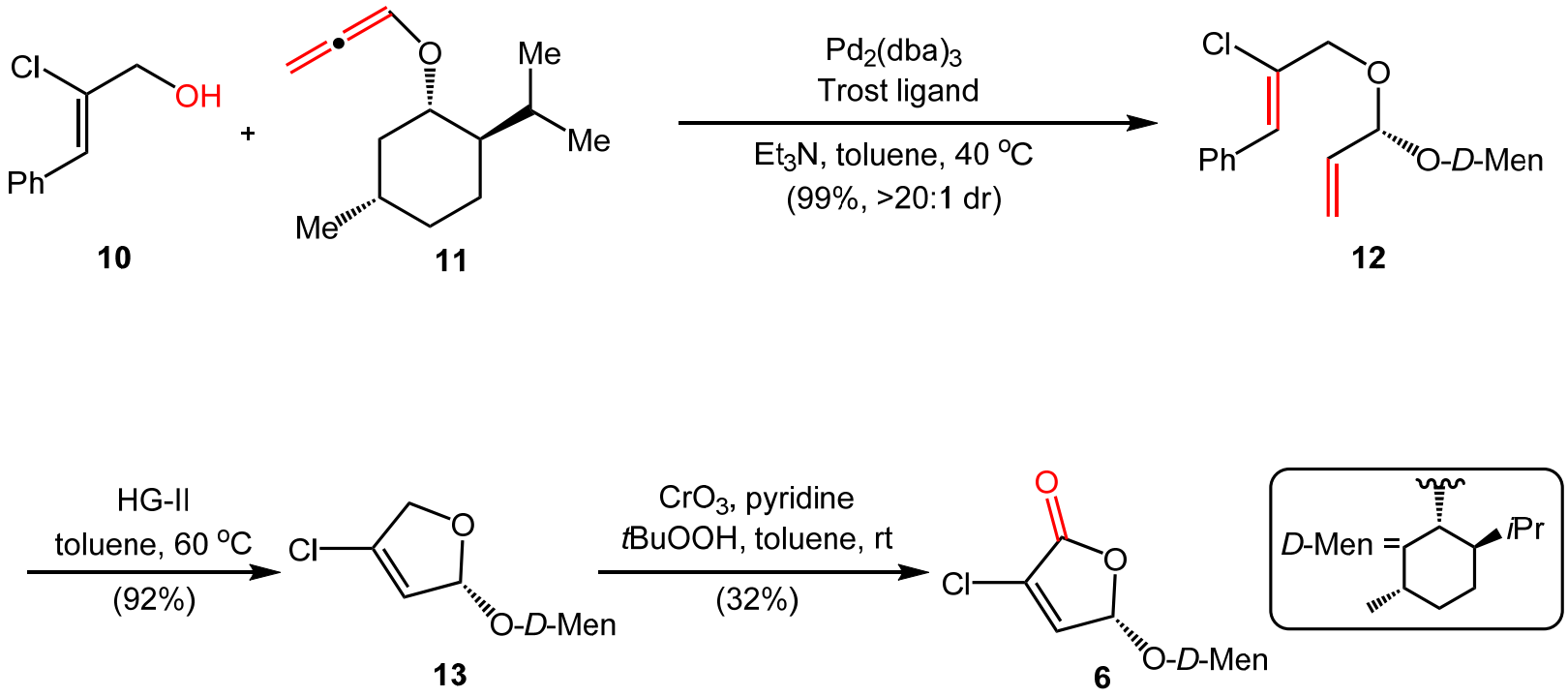


5 **7** **8** **9**

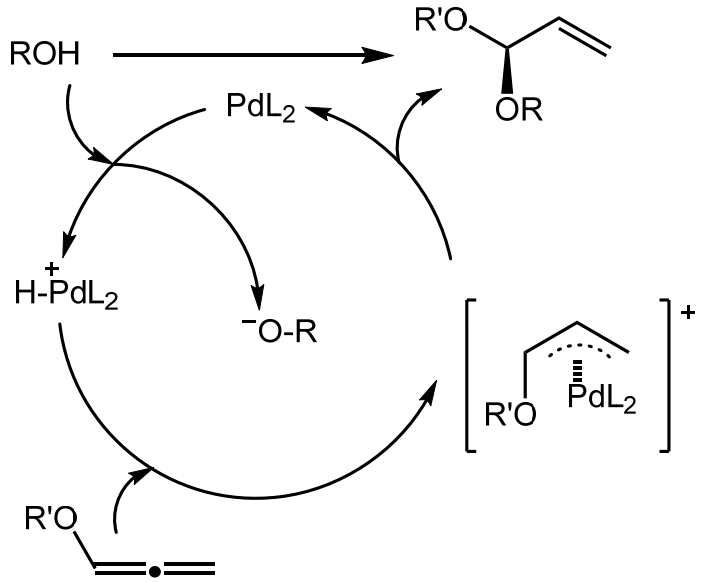


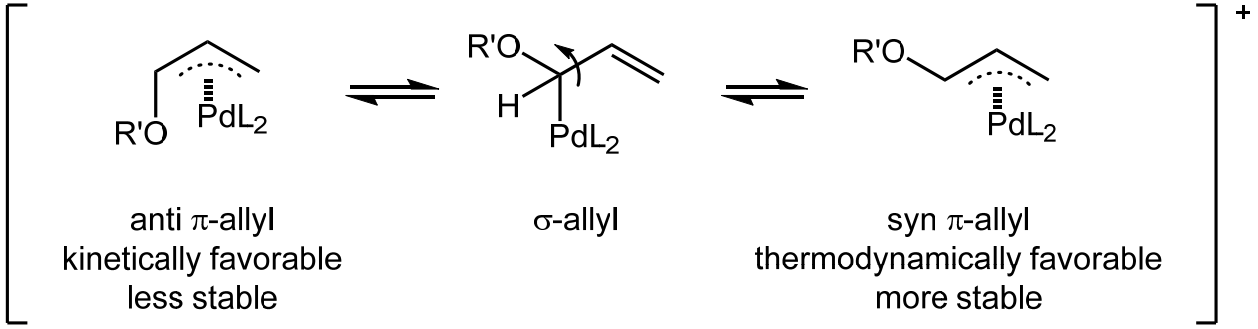
6 **10** **11**

Synthesis of Fragment 6



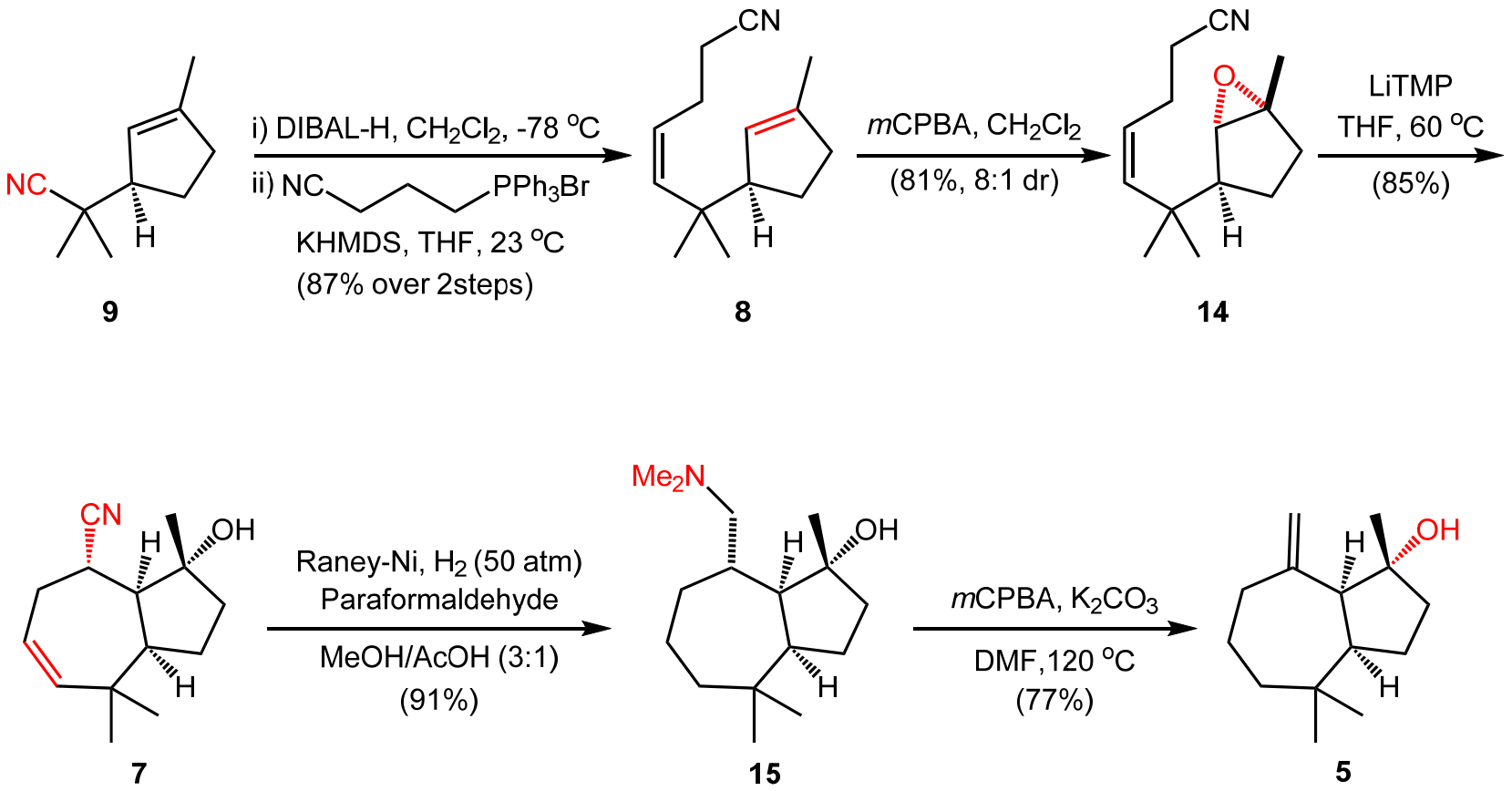
Allene Hydroalkoxylation Mechanism



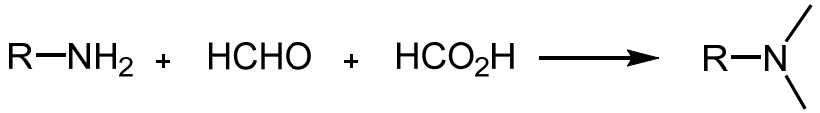


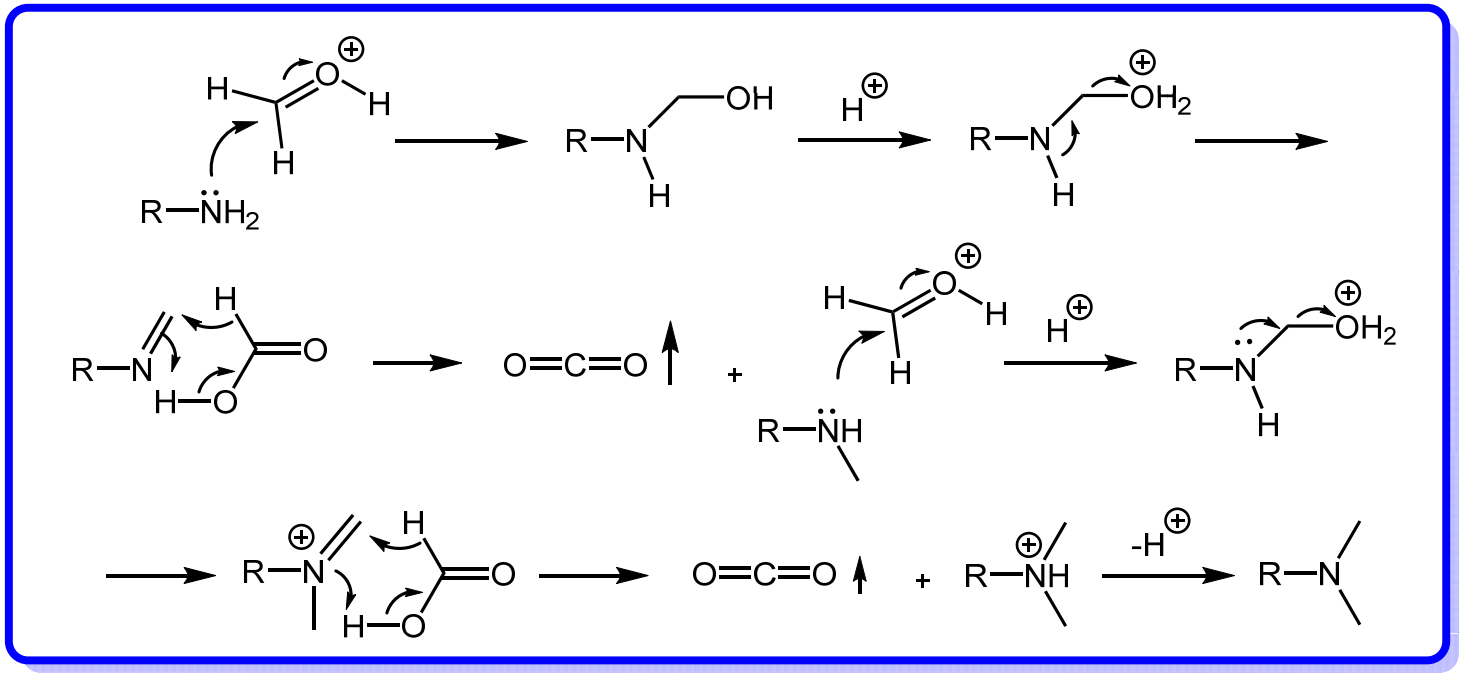
Lim, W.; Kim, J.; Rhee, Y. H. *J. Am. Chem. Soc.* ***2014***, *136*, 13618

Synthesis of (+)-Cheloviolene A



Eschweiler–Clarke reductive alkylation

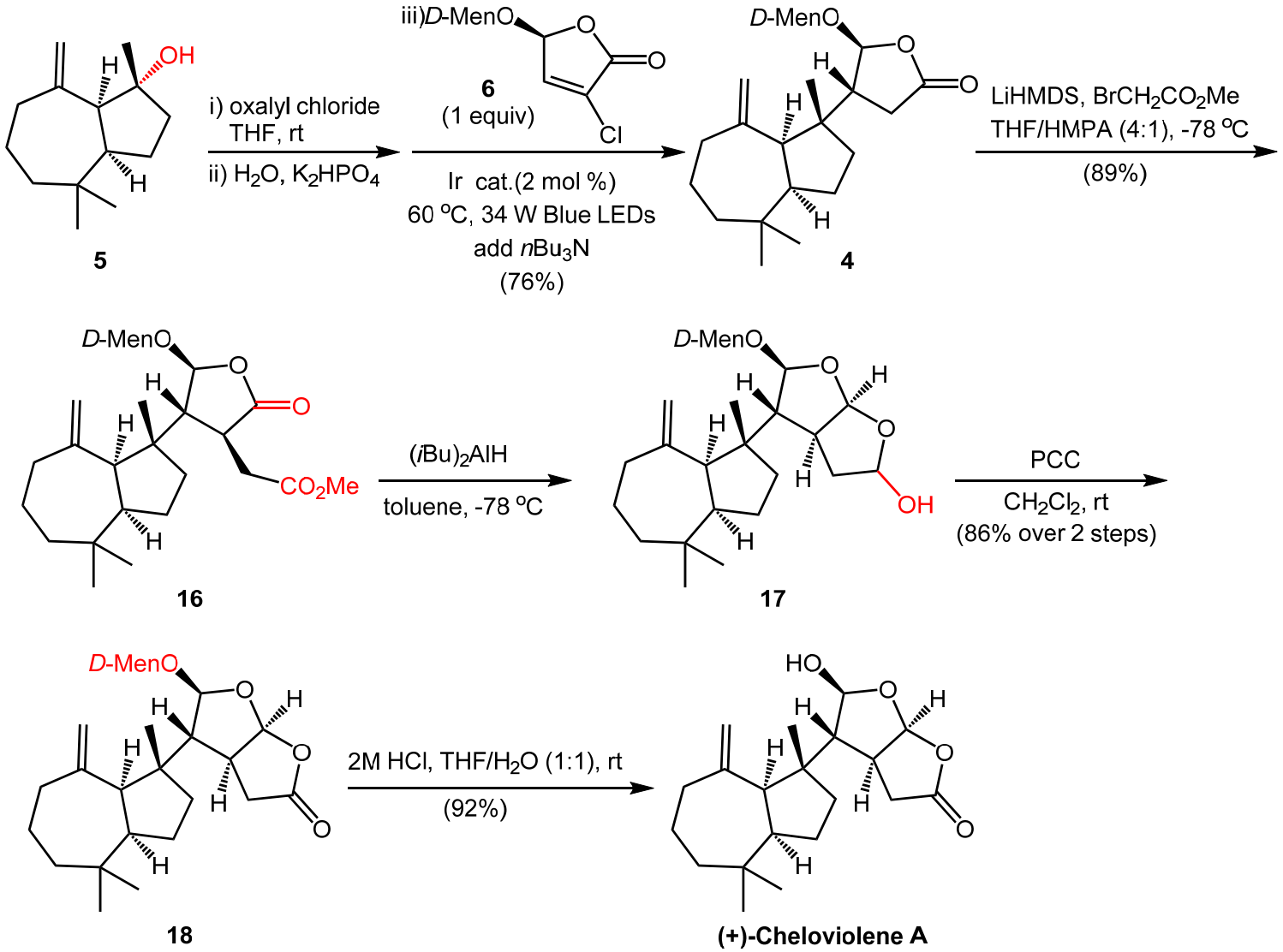




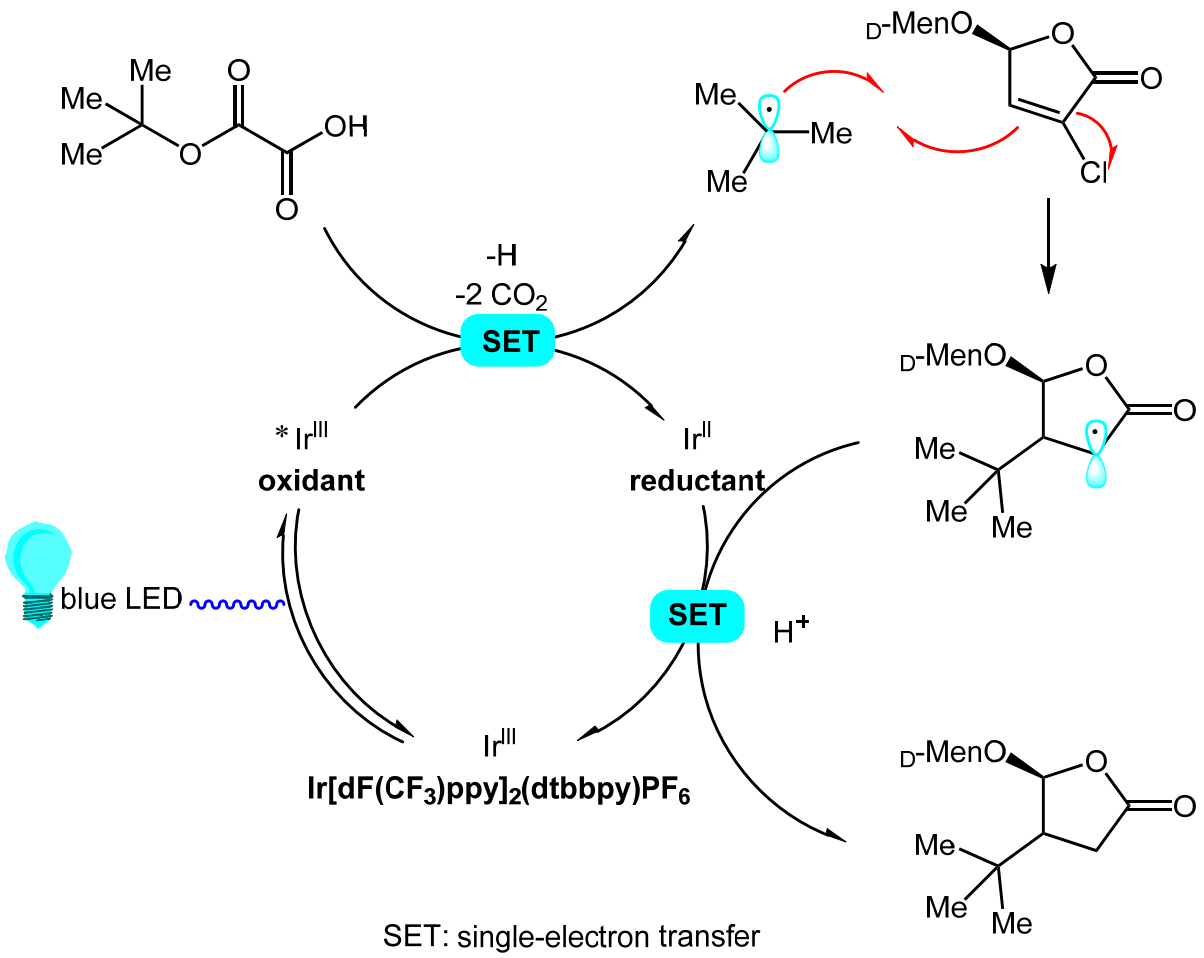
Eschweiler, W. *Chem Ber*. **1905**, *38*, 880

Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z.; *J. Am. Chem. Soc.* **1933**, *55*, 4571

Synthesis of (+)-Cheloviolene A

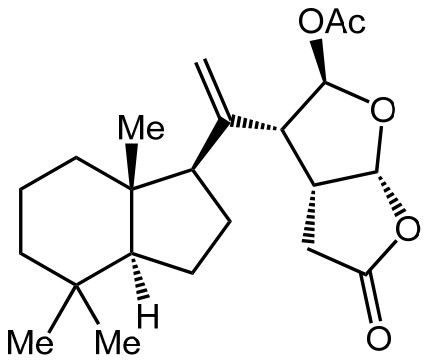


Radical-Coupling Reaction Mechanism



Nawrat, C. C.; Jamison, C. R.; Overman, L. E. *J. Am. Chem*. Soc. **2015**, *137*, 11270

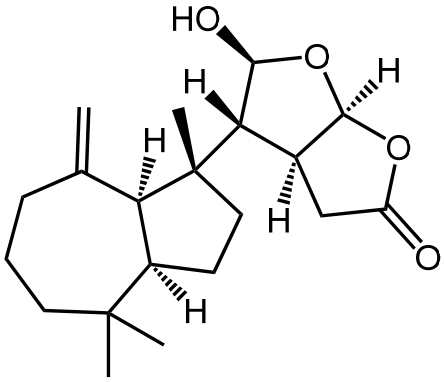
Summary



(+)-Norrisolide

- 13 Steps, 1.58% overall yield;
- The first total synthesis of Norrisolide;
- Diels-Alder reaction;
- The union of fragments **3** and **4**.

Brady, T. P.; Kim, S. H., Theodorakis, E. A. *Angew. Chem. Int*. Ed. **2004**, *43*, 739



(+)-Cheloviolene A

- 11 Steps, 20.2% overall yield;
- The first total synthesis of Cheloviolene A;
- High-yielding fragments coupling;
- Established the absolute configuration.

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The First Paragraph Structure

- Where the dioxabicyclic ring comes from ;
- Some examples about this structure skeleton;
- The structure of dioxabicyclo[3.3.0]octan-3-one;
- The significance of total synthesis of 6-substituted dioxabicyclo[3.3.0]octan-3-one.

The First Paragraph

The *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one (**1**) ring system is found in nearly 100 natural products. In a subset of these, the dioxabicyclic ring is isolated and joined at C-6 to a hydrocarbon fragment of nine or fourteen carbons. The fungal sesquiterpenoid **2** is an example of the former group, whereas diterpenoids **3-8** exemplify the larger group that were isolated from marine sponges or nudibranchs. Norrisolide (**3**) was the first of these natural products to be described. In the more common members of this group, the dioxabicyclo[3.3.0]octan-3-one fragment is attached to a quaternary carbon of the hydrocarbon unit, for example diterpenoids **4**-**8**.

The First Paragraph

Two distinct structural subtypes that differ in whether the hydrocarbon fragment resides on the concave or convex face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment, exemplified respectively by dendrillolide A (**5**) and cheloviolene A (**6**), are observed. The relative configurations of norrisolide (**3**), macfarlandin C (**4**) and cheloviolene A (**6**) are known by virtue of single-crystal X-ray analyses. The absolute configuration of norrisolide (**3**) was established by Theodorakis' inaugural total synthesis, whereas that of rearranged spongian diterpenoids **4-8** and structurally related natural products has not been established. They are suggested to be as depicted in Figure **1** by virtue of their presumed biosynthesis from precursors having a spongian skeleton (**9**).

The Last Paragraph Structure

- Overview;
- The key methods involved in this total synthesis;
- The results or the achievements;
- The meaning of constructing 6-substituted dioxabicyclo[3.3.0]octan-3-one.

The Last Paragraph

In summary, a five-step enantioselective sequence to prepare 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones was developed. High-yielding fragment coupling of a tertiary radical generated directly from a tertiary alcohol with an enantiopure 3-chloro-5-alkoxybutenolide in which both precursors are used in equimolar amounts is the pivotal step of this synthetic strategy. This sequence was exemplified by short syntheses of (+)-cheloviolenes A and B and (+)-dendrillolide C, which established the absolute configuration of these diterpenoid natural products and corrected the structural assignment for cheloviolene B. This rapid and versatile construction of the 6-substituted-*cis*-2,8-dioxa-bicyclo[3.3.0]octan-3-ones should aid in future studies of biological activity of molecules harboring this ring system.

Acknowledgement

Thanks
for your attention