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Article

Total Synthesis of (+)-Cyclobutastellettolide B

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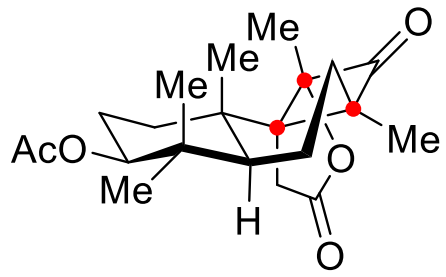
Jiangpeng Liu
Liu Research Group
12/10/2021

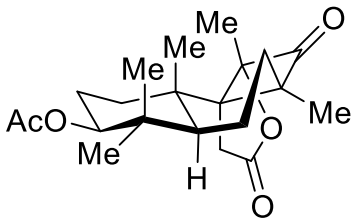


Cyclobutastellettolide B

Introduction:

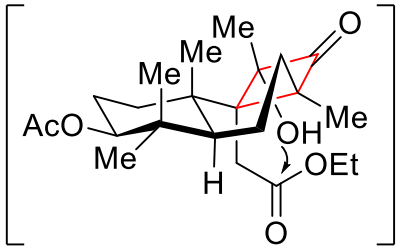
- Cyclobutastellettolide B was originally isolated from a Stelletta sp. sponge (3.0 mg/1.3 kg) by Stonik et al. in 2019.
- It could significantly increase the reactive oxygen species level in murine peritoneal macrophages and be a potential lead for the development of immunomodulatory agents.
- It has an unusual 6/6/4-fused tricyclic core with six stereocenters. Among them, three are contiguous quaternary stereocenters.
- The first enantioselective total synthesis of (+)-cyclobutastellettolide B in 13 steps with a total yield of 31.5%.

Retro-synthetic route

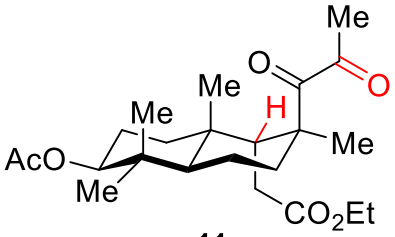


Cyclobutastellettolide B

lactonization



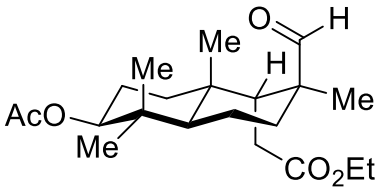
Norrish-Yang cyclization



11

olefination &

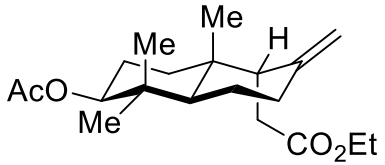
oxidation



7

oxidation &

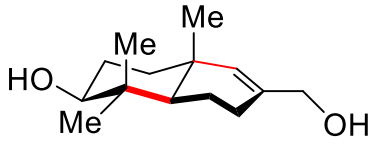
alkylation



4

Johnson-Claisen

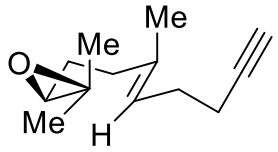
rearrangement



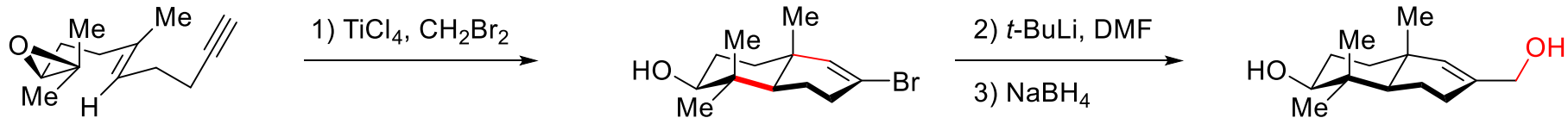
3

polycyclization &

hydroxymethylation



1

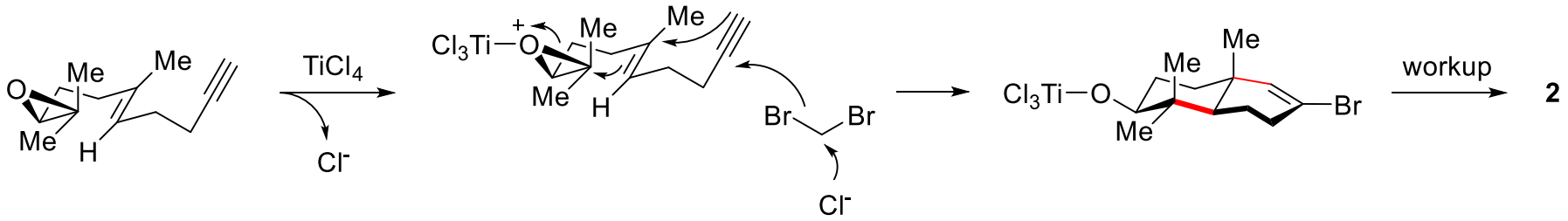


1
97% ee

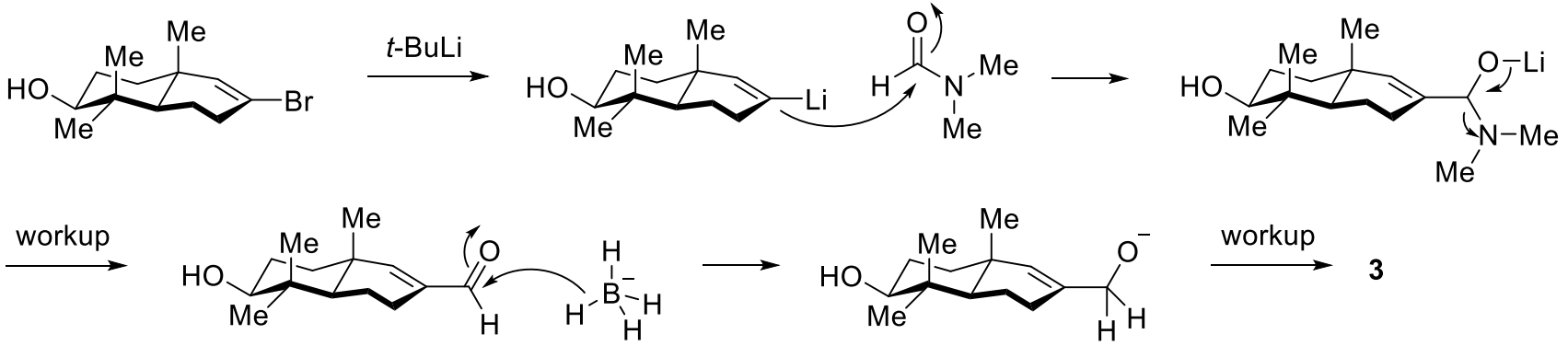
2
86%

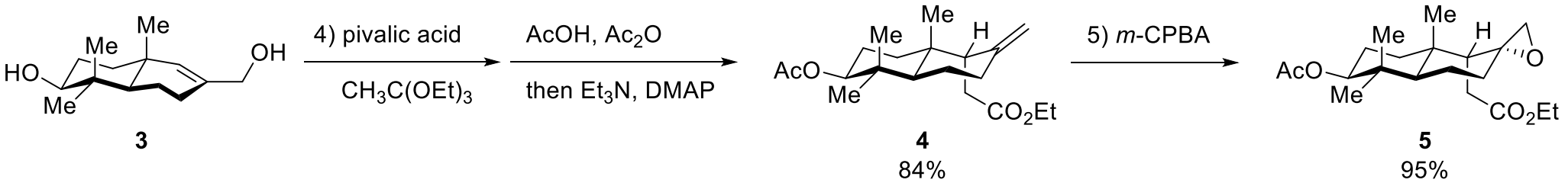
3
92% in 2 steps

Polycyclization of epoxide:

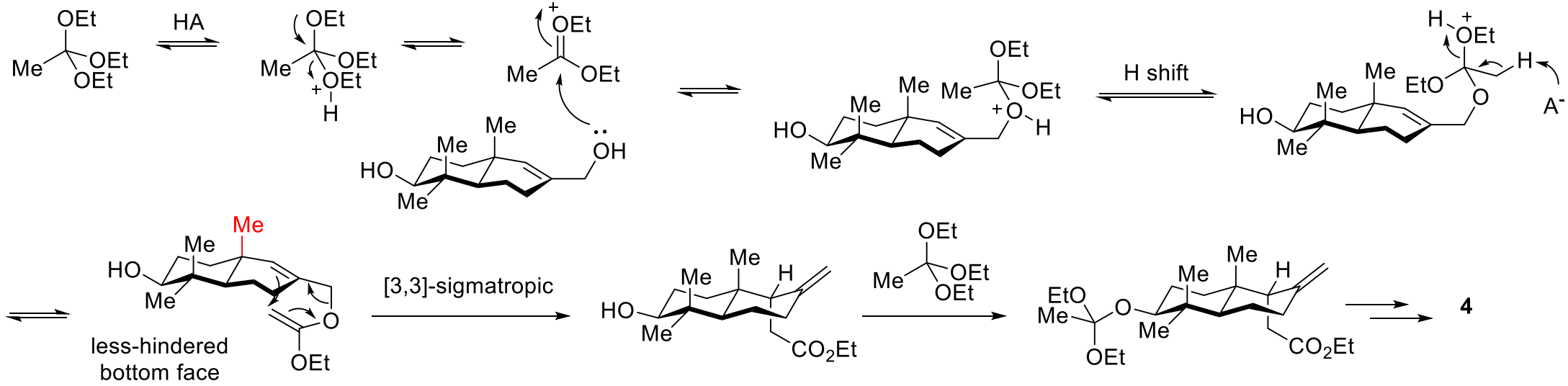


Vinyllithium formation and DMF as carbonyl source:

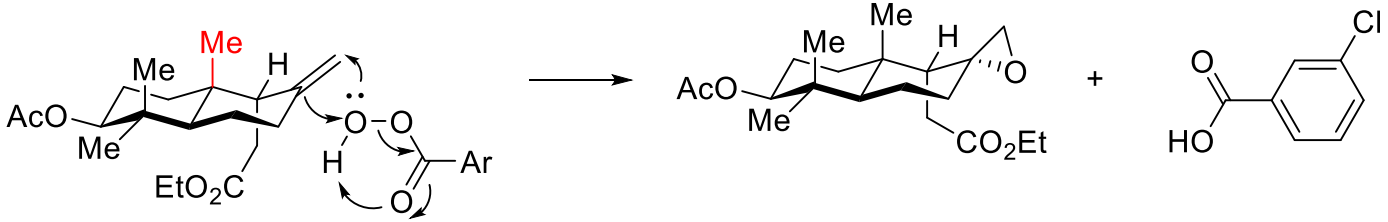


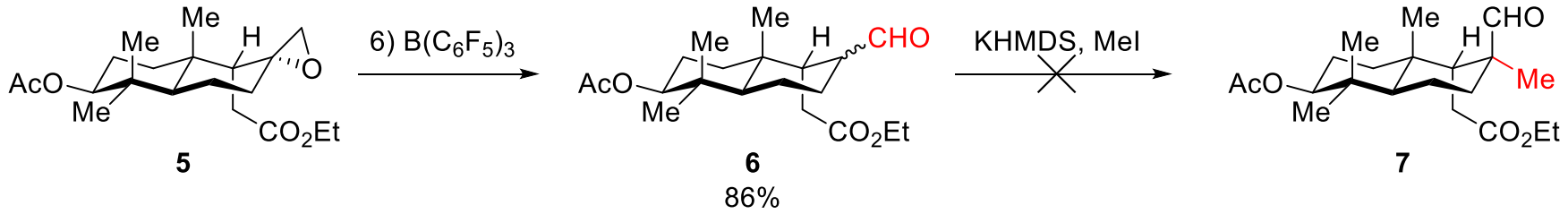


Johnson-Claisen rearrangement:

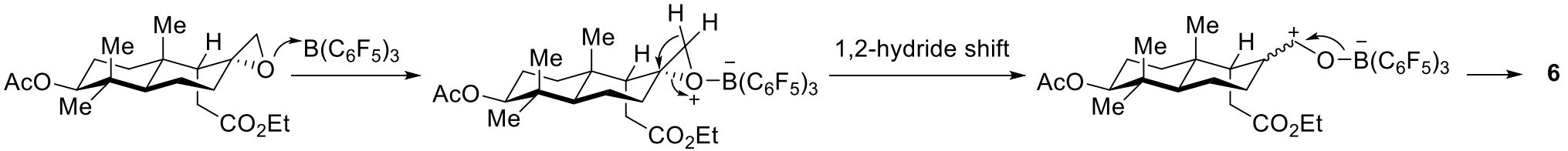


Prilezhaev epoxidation:

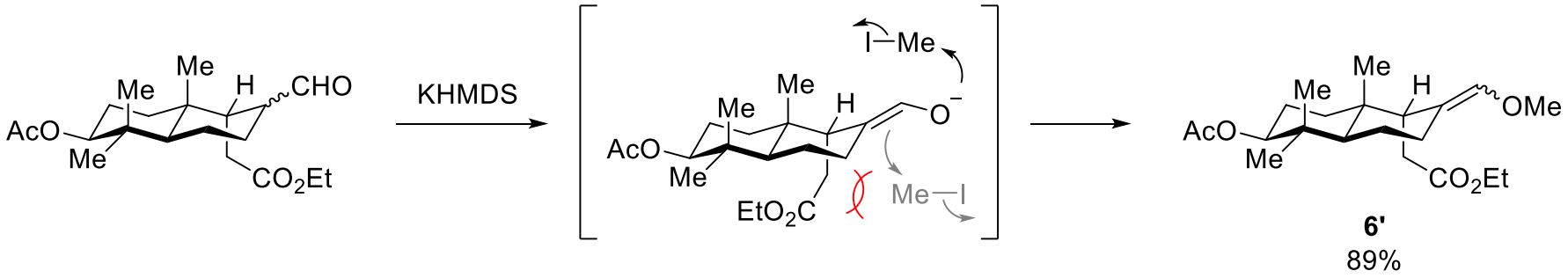


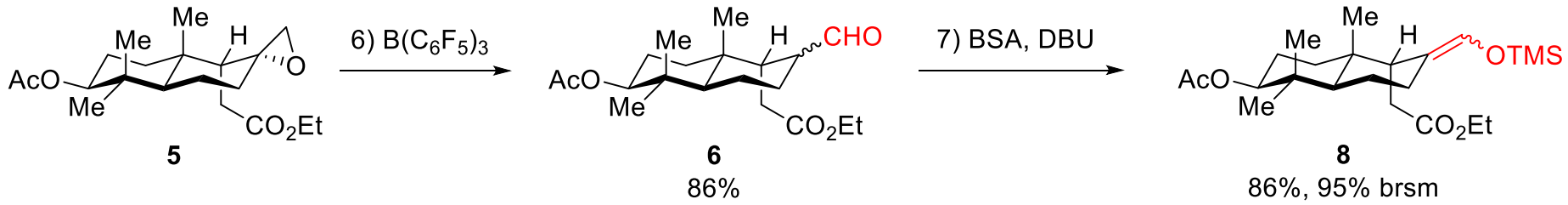


Lewis acid mediated epoxide ring-opening:

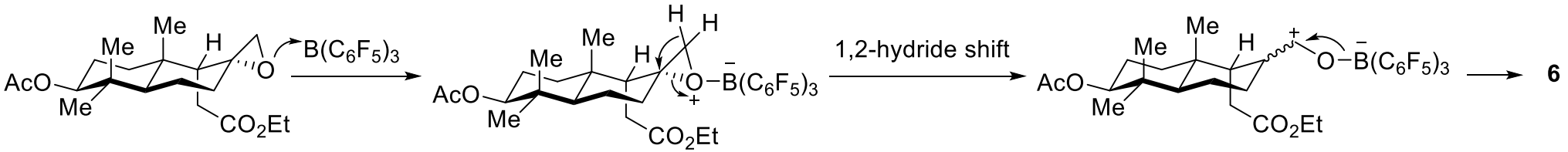


Direct methylation of aldehyde:

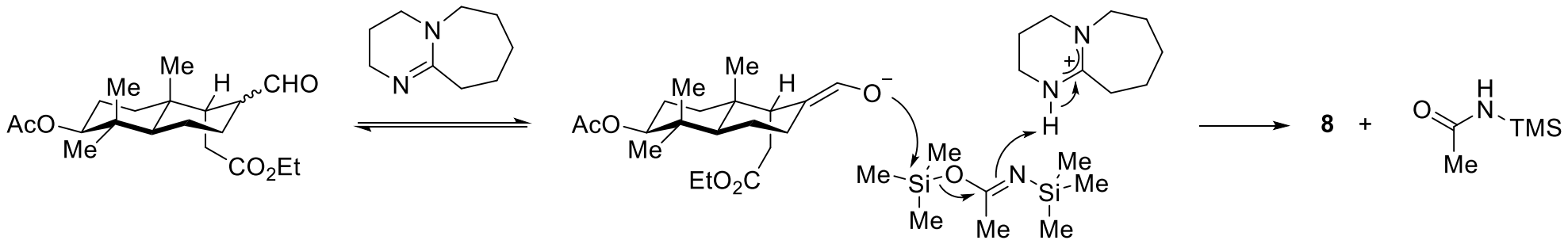




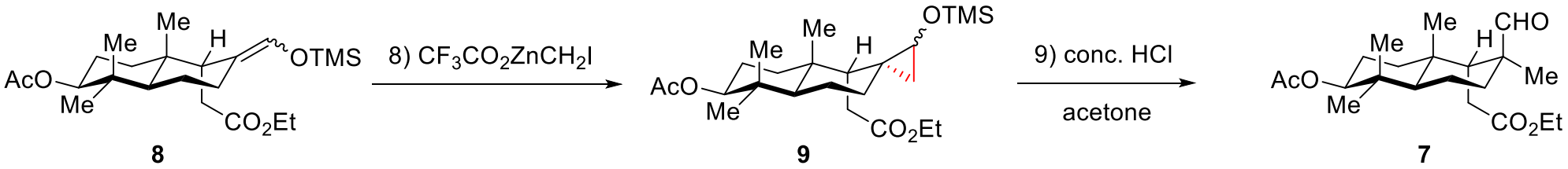
Lewis acid mediated epoxide ring-opening:



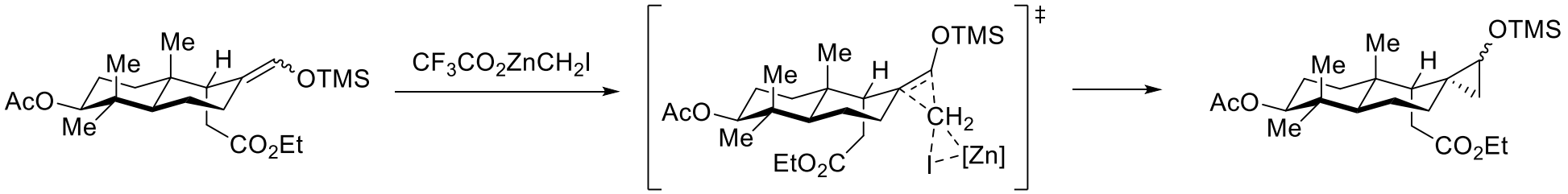
Formation of silyl enol ether:



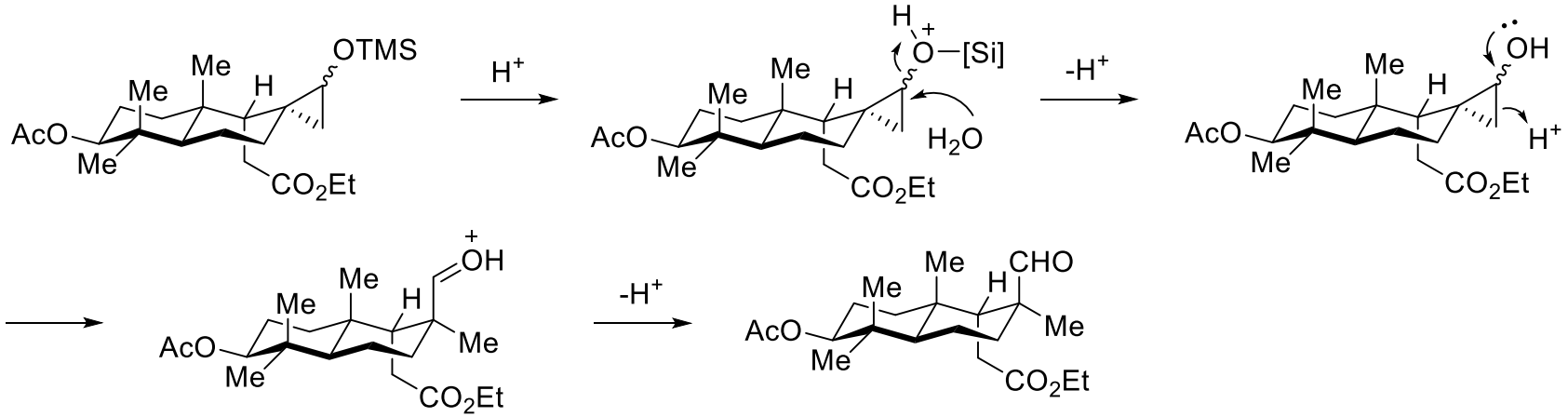
Bis(trimethylsilyl)acetamide

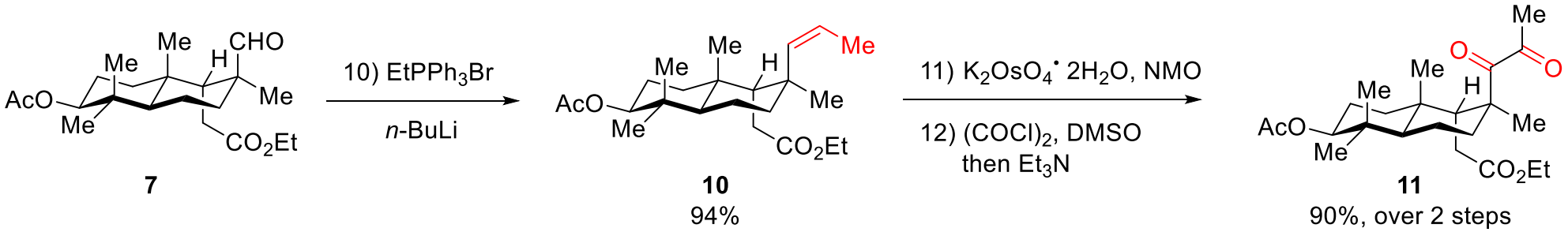


Simmons-Smith cyclopropanation:

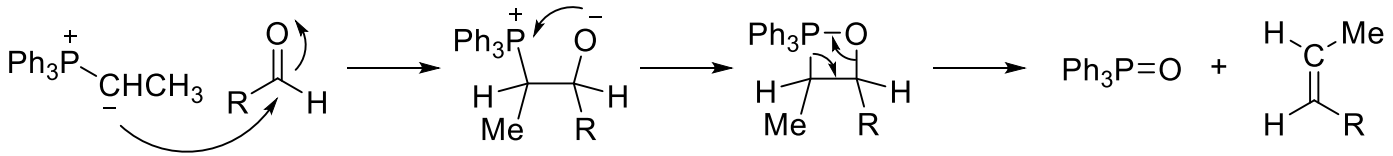


Acid-mediated regioselective ring-opening reaction:

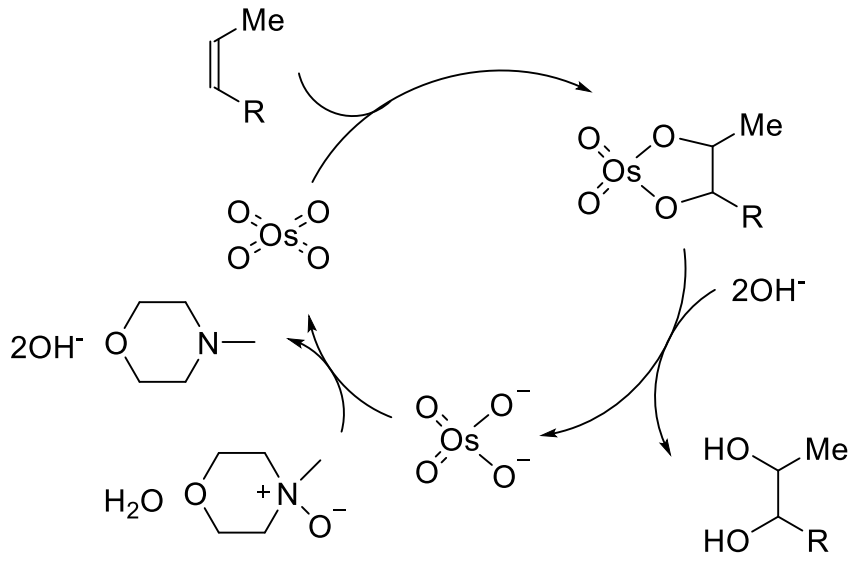




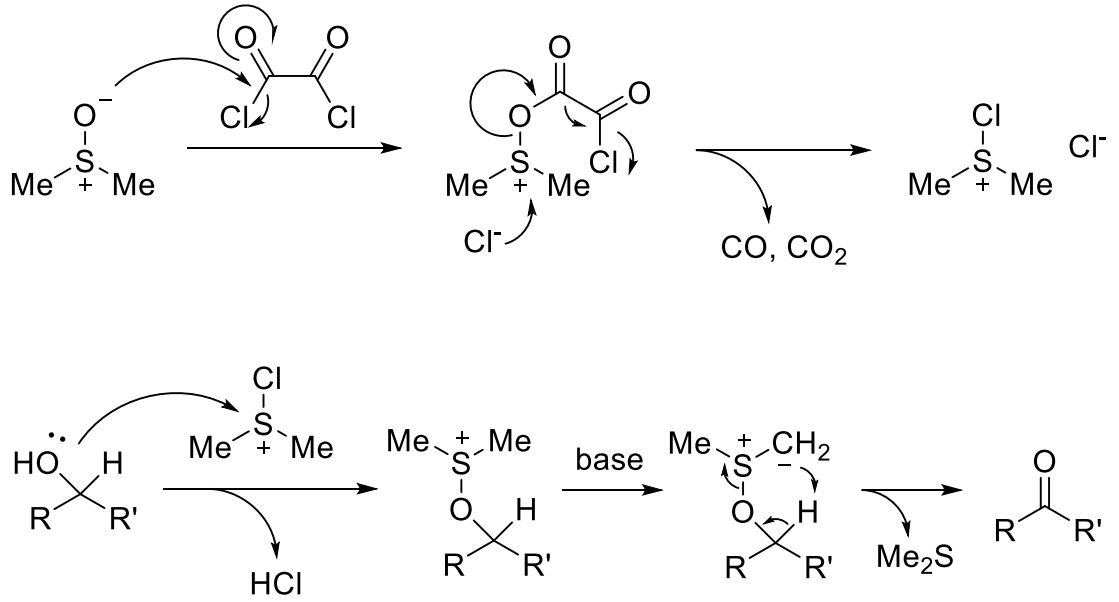
Wittig reaction:

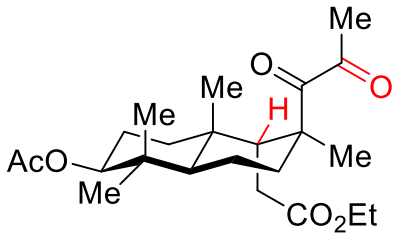


Upjohn dihydroxylation:



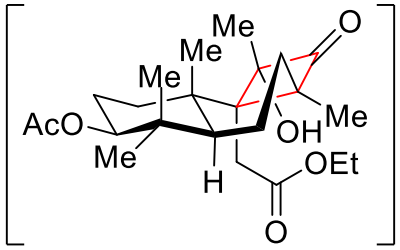
Swern oxidation:





11

13) CFL or white light



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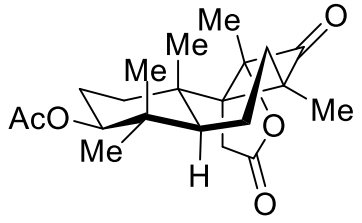
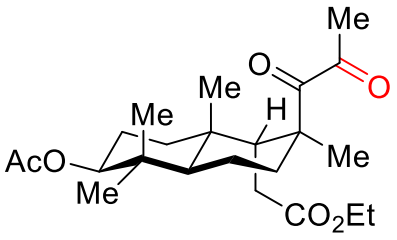


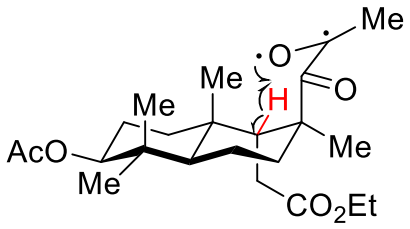
Cyclobutastellettolide B

95%

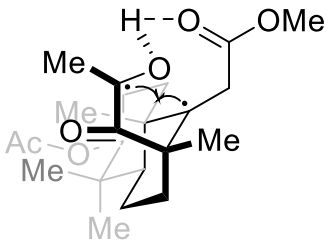
Norrish-Yang photocyclization:



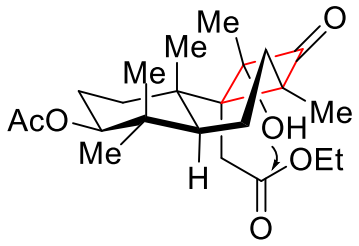
hv



1,5-HAT



intramolecular recombination



lactonization

Cyclobutastellettolide B

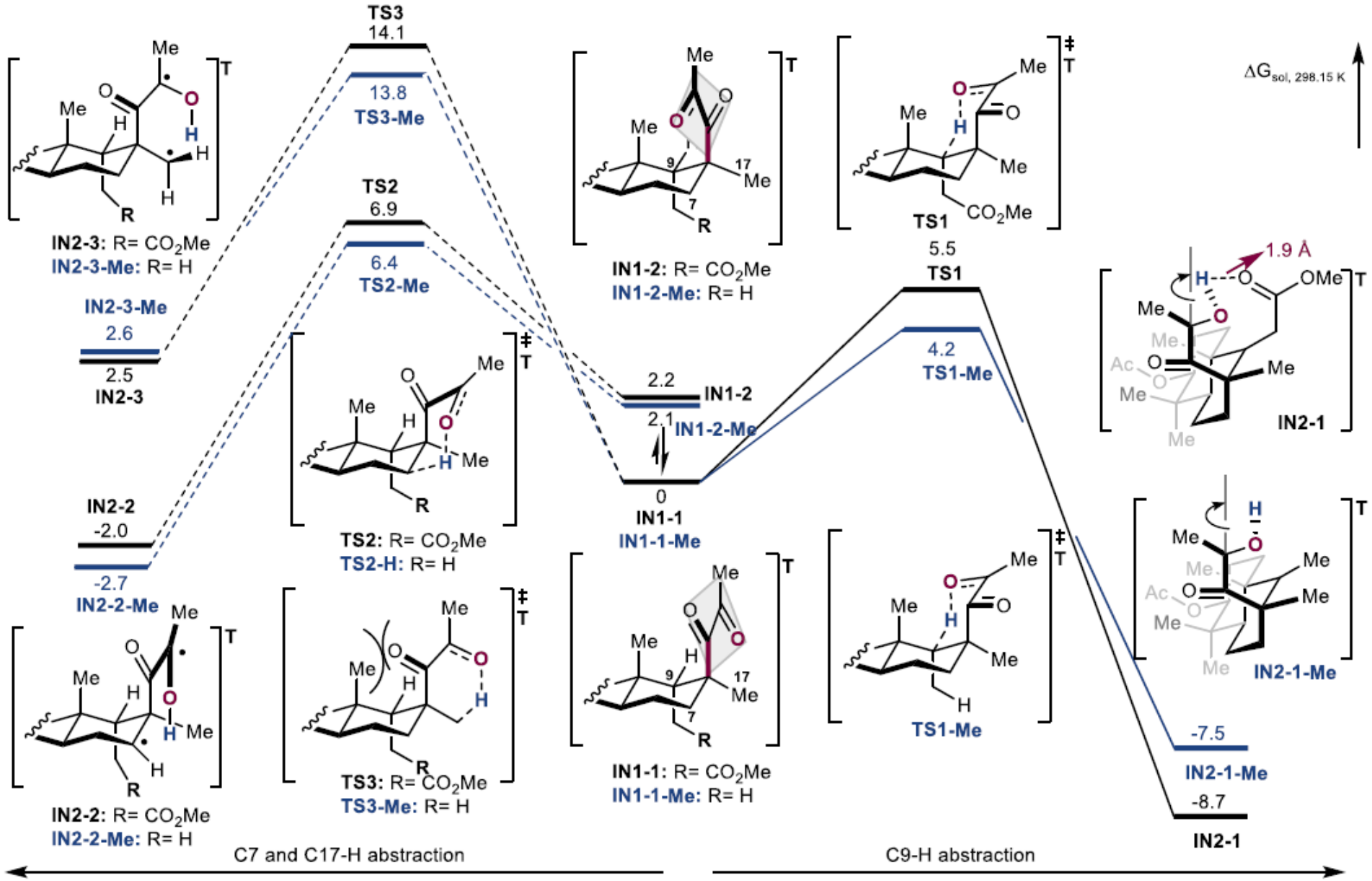
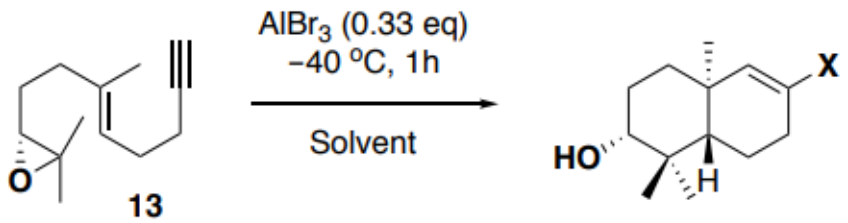


Figure S2. Energy profiles of 1,5-hydrogen shift of **IN1-1 and IN1-1-Me** via C9-H, C7-H and C17-H abstraction.

Thanks for your attention

3. Experiments on the Source of the Halogen Atom

In order to know about the source of the bromine atom (CH_2Br_2 versus $AlBr_3$) in the cyclization reaction of epoxy-containing enyne **(+)-13** to get **(–)-1** we performed the following reactions with $AlBr_3$ as promoter and dichloromethane or iodomethane as solvents. As shown, in these experiments we obtained the corresponding chloride or iodide derivatives and we did not observe the formation of the corresponding bromide derivative **1**. This seems to demonstrate that the halogen always comes from the solvent.



13

Solvent	
$CH_2\mathbf{Br_2}$	**1** (X = Br); 83%
$CH_2\mathbf{Cl_2}$	**14** (X = Cl); 70%
$CH_3\mathbf{I}$	**15** (X = I); 74%

Fontaneda, R.; Fañanás, F. J.; Rodríguez, F. *Chem. Commun.* **2018**, *54*, 11025–11028.