Total Synthesis of (–)-Crinipellin A

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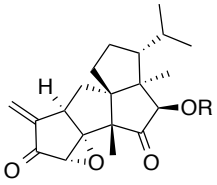
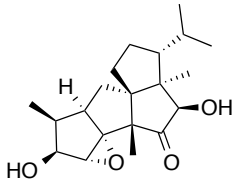
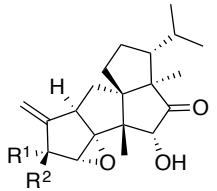
I. Introduction



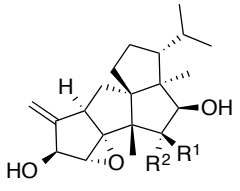
1 - crinipellin A, R = H
2 - *O*-acetylcrinipellin A, R = Ac



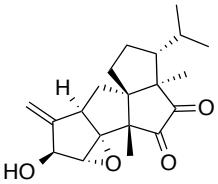
3 - tetrahydrocrinipellin A



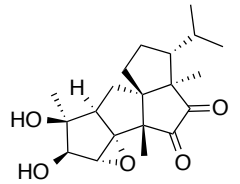
4 - crinipellin B, R^1,R^2 = O
5 - dihydrocrinipellin B, R^1 = H, R^2 = OH



6 - dihydrocrinipellin A, R^1,R^2 = O
7 - tetrahydrocrinipellin B, R^1 = H, R^2 = OH



8 - crinipellin C



9 - crinipellin D

- Crinipellins (**1 – 5**) were first isolated from the basidiomycete *Crinipellis stipitaria* in 1979.
- These compounds display antibacterial and anticancer activity.
- Compounds **6 – 9** were isolated late from a different fungal strain, *Crinipellis* sp. 113 and only show moderate anticancer activity.
- These are the only known class of tetraquinane natural products.
- Only previously reported total synthesis of a crinipellin natural product is Piers' report of the total synthesis of crinipellin B[1].

1. Kang, T.; Song, S. B.; Kim, W.-Y.; Kim, B. G.; Lee, H.-Y. *J. Am. Chem. Soc.* **2014**, *136*, 10274–10276.

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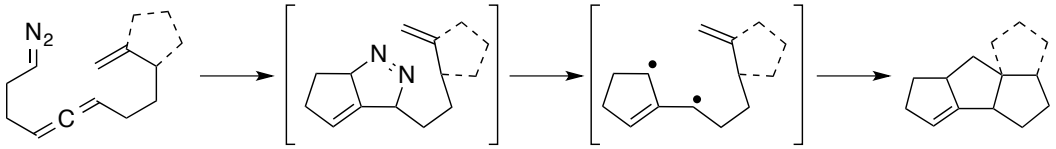
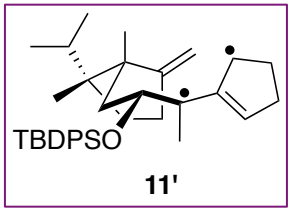
II. Synthetic Considerations



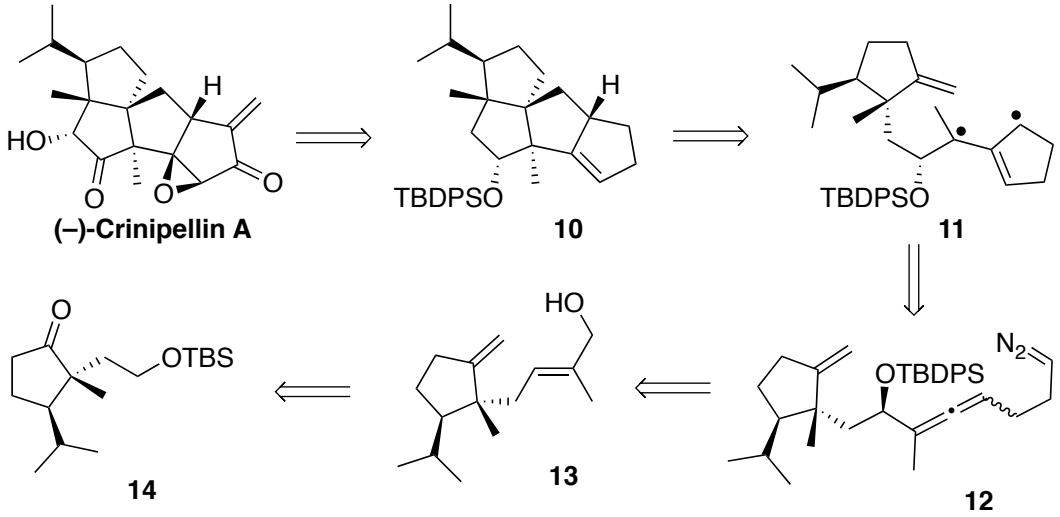
Extension of TMM strategy to tetraquinane

- Eight contiguous stereocenters
- Tetraquinane skeleton
- Utilize their recently reported synthetic methodology for triquinane synthesis from acyclic substrates.

III. Retrosynthetic Analysis



11'



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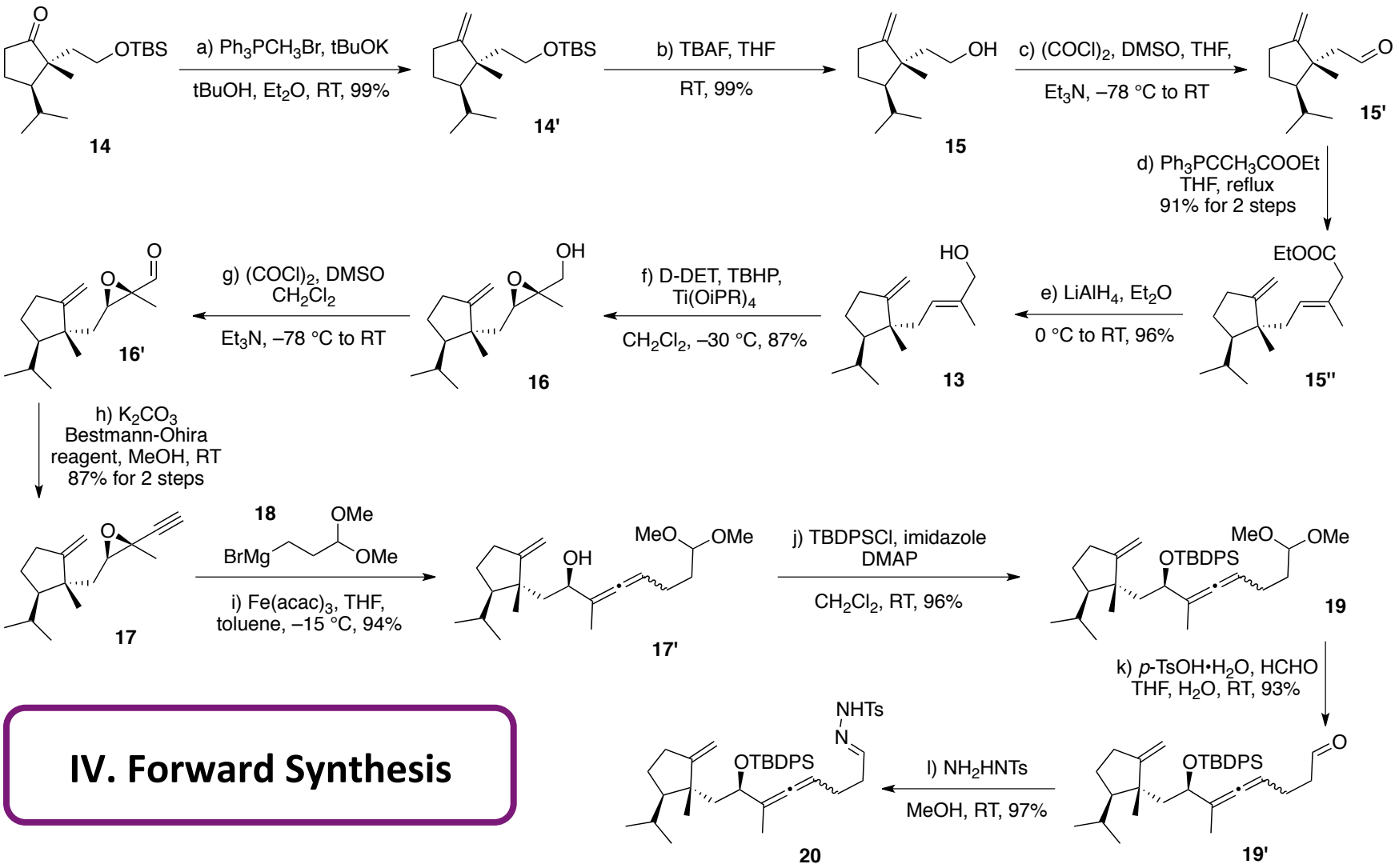
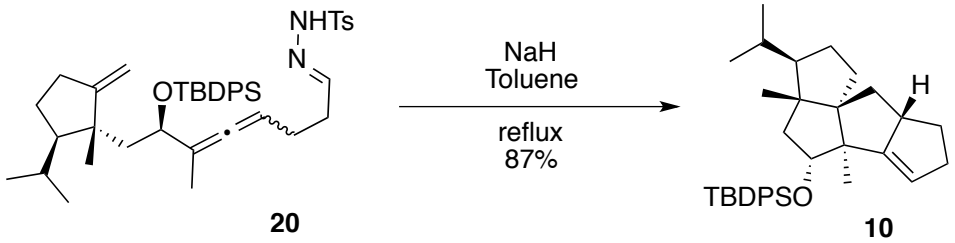
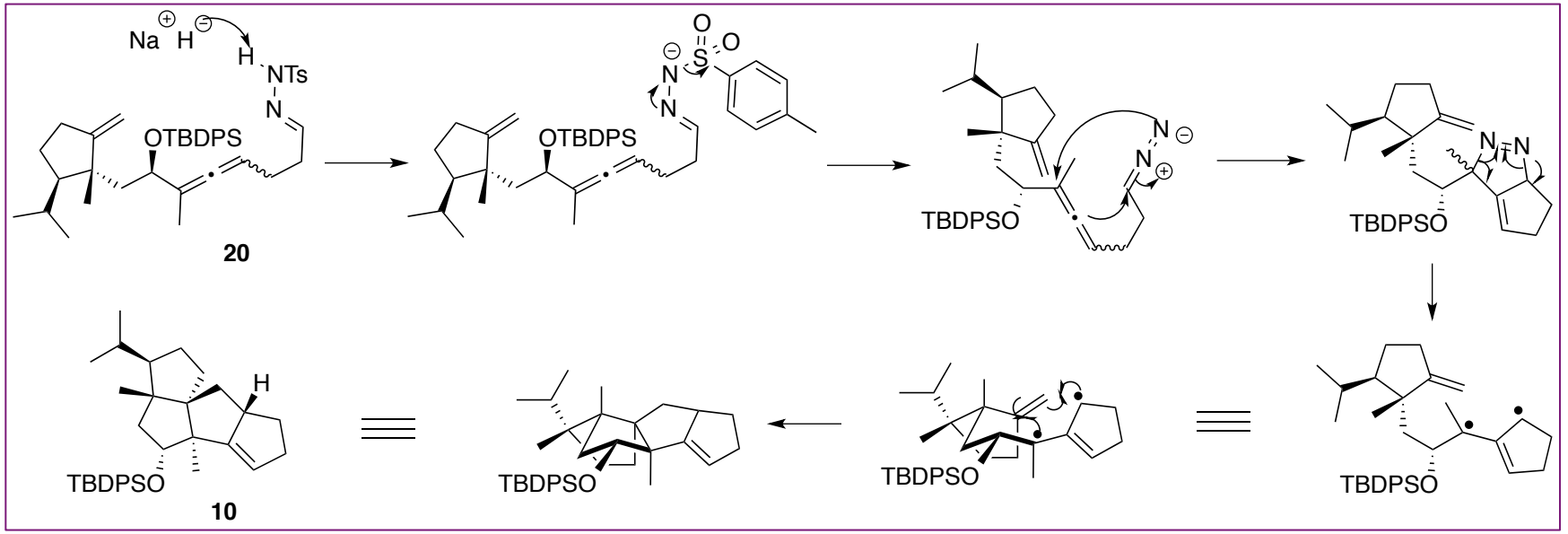


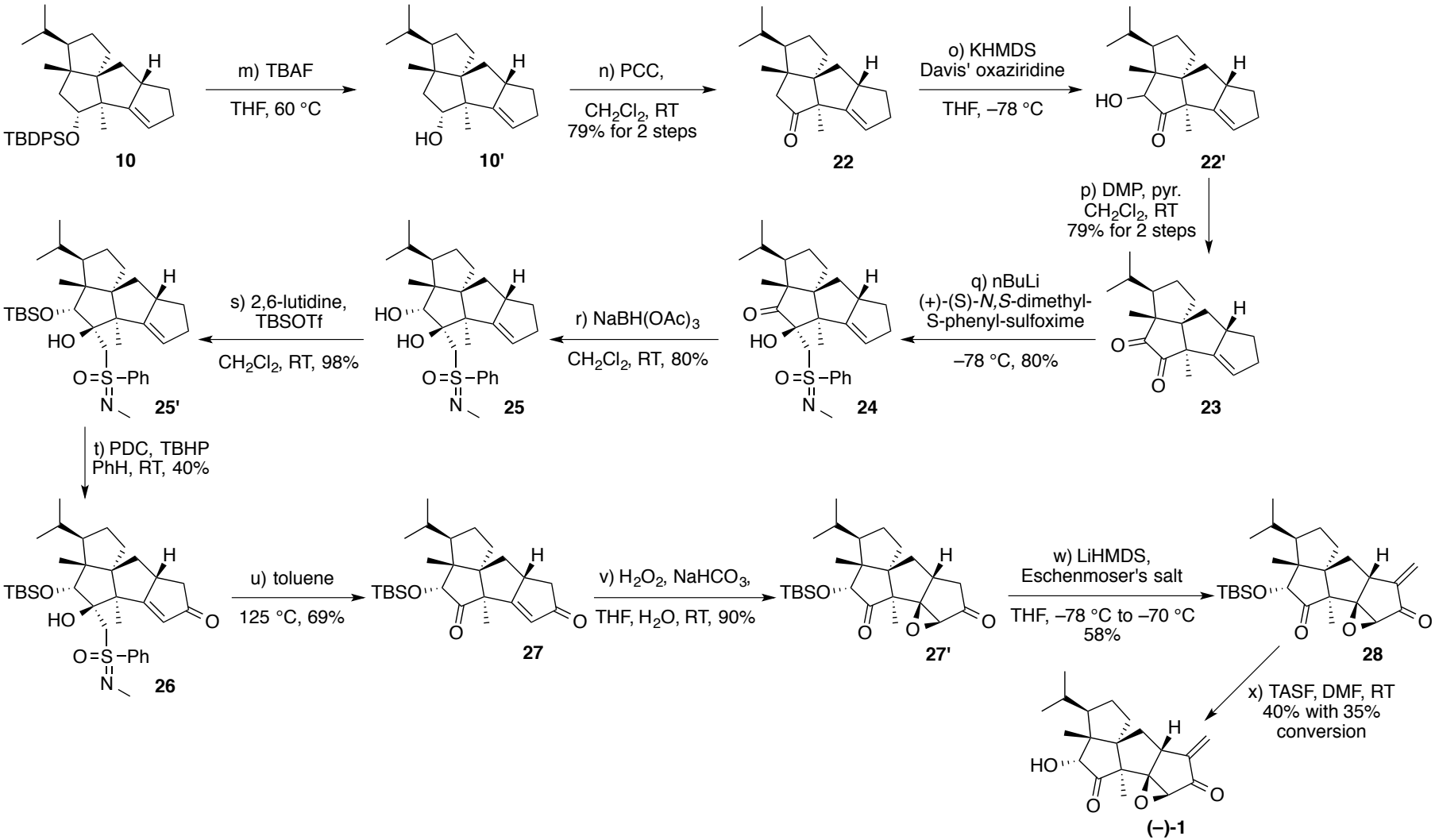
IV. Forward Synthesis

Total Synthesis of (–)-Crinipellin A





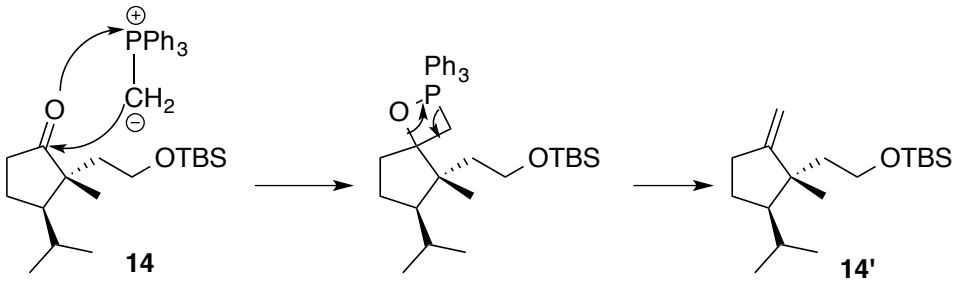
Total Synthesis of (–)-Crinipellin A



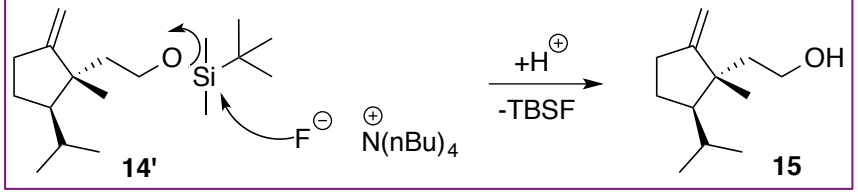
Total Synthesis of (–)-Crinipellin A

V. Mechanisms

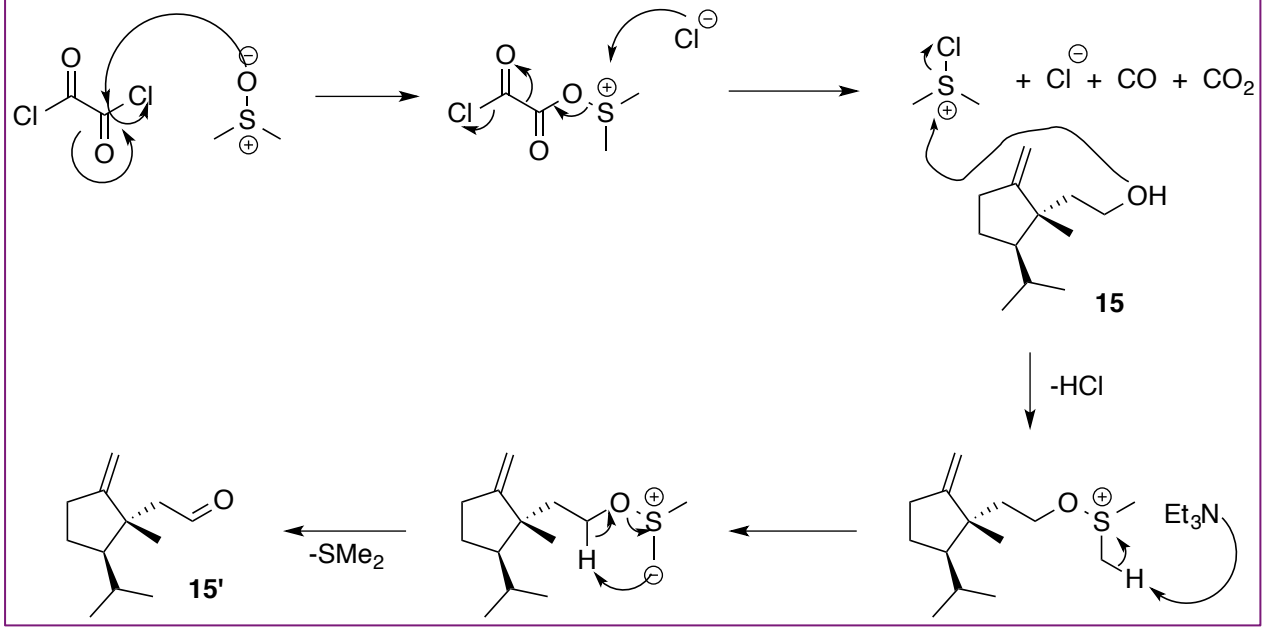
Mechanism a: Wittig olefination



Mechanism b: TBS deprotection



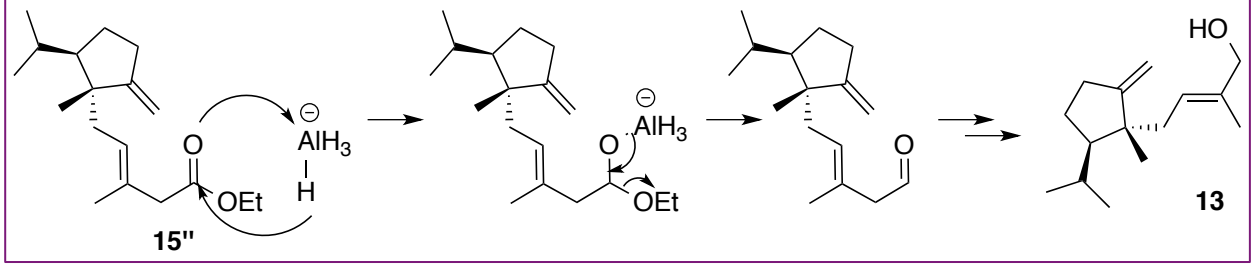
Mechanism c: Swern oxidation



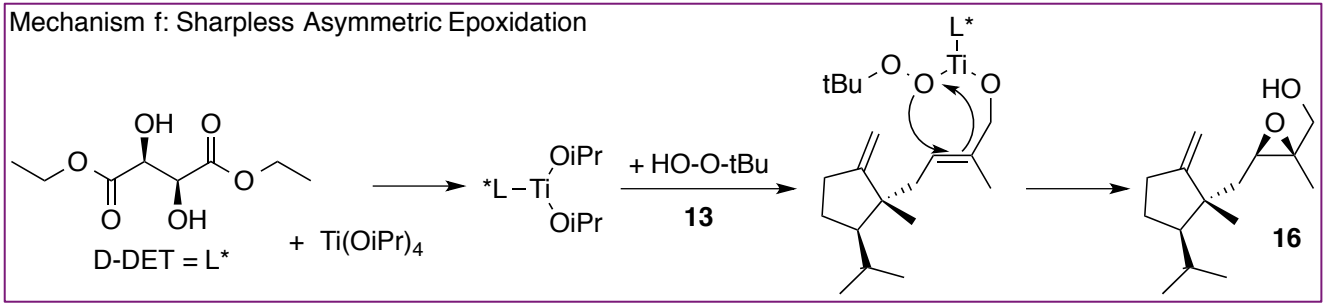
Total Synthesis of (–)-Crinipellin A

Mechanism d: Horner-Wadsworth-Emmons olefination
See mechanism a

Mechanism e: LAH reduction

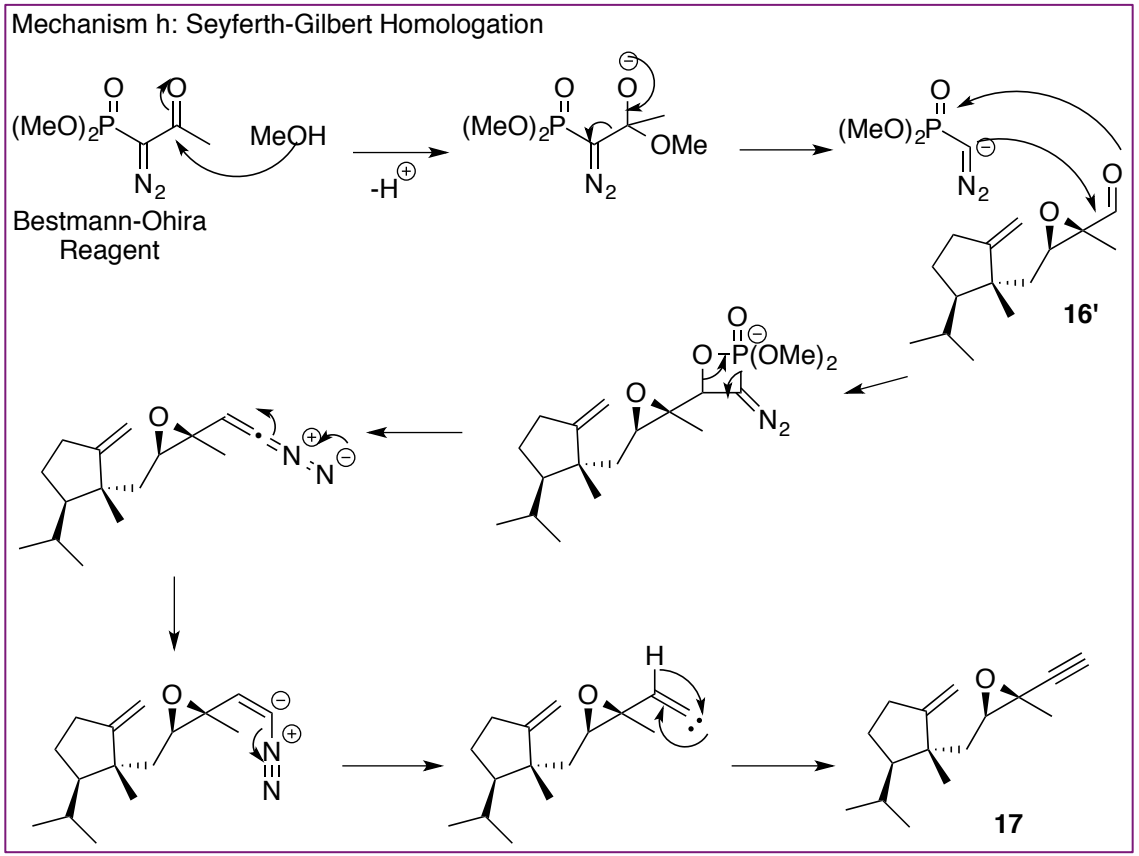


Mechanism f: Sharpless Asymmetric Epoxidation



Mechanism g: Swern oxidation
See mechanism c

Total Synthesis of (–)-Crinipellin A



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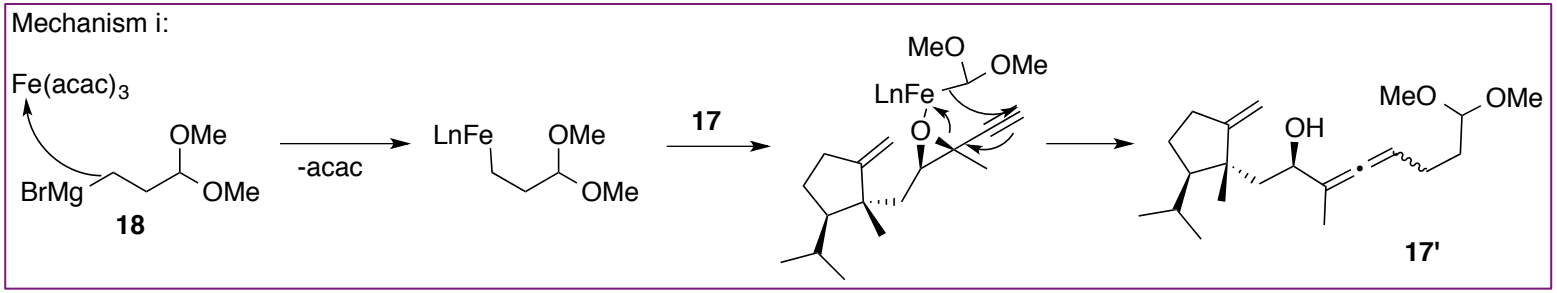
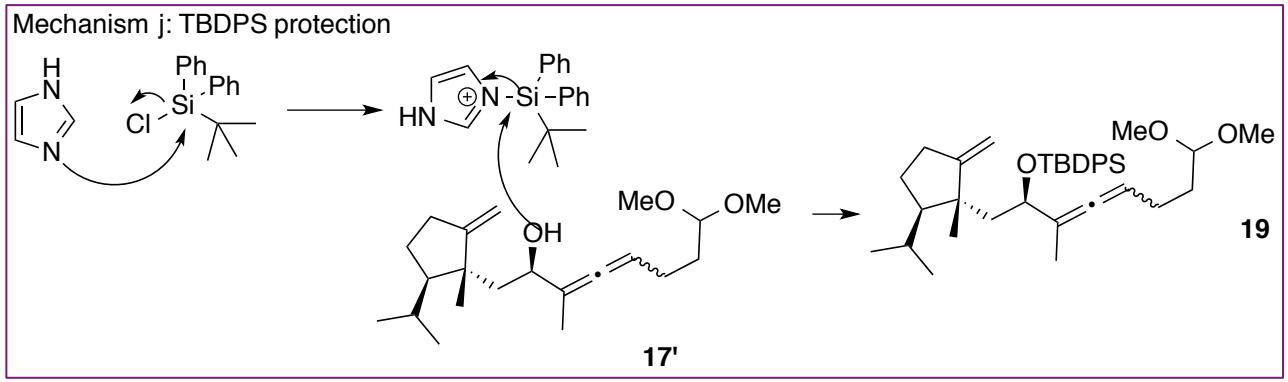
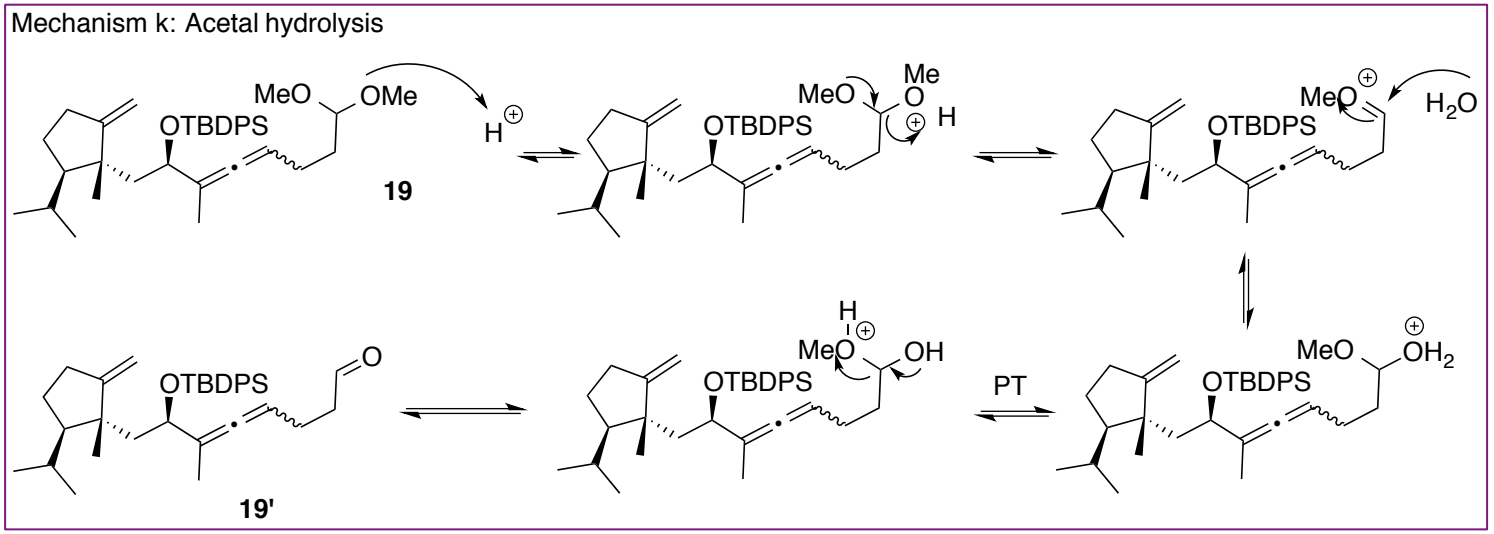
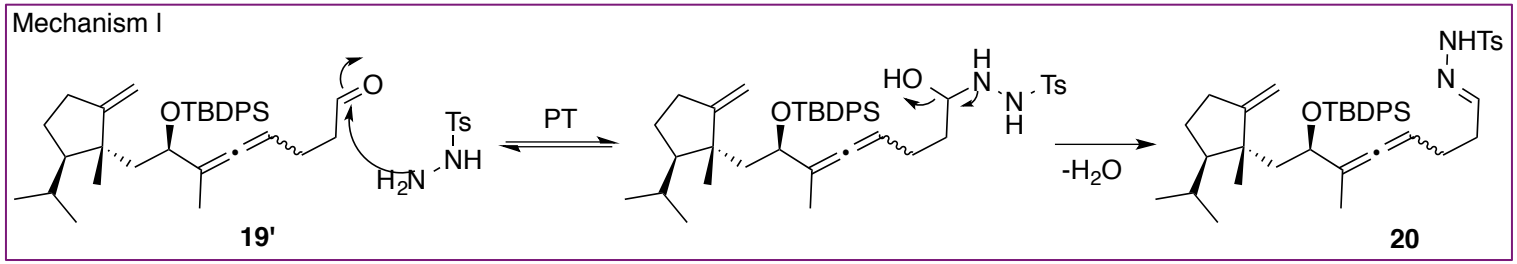




Total Synthesis of (–)-Crinipellin A





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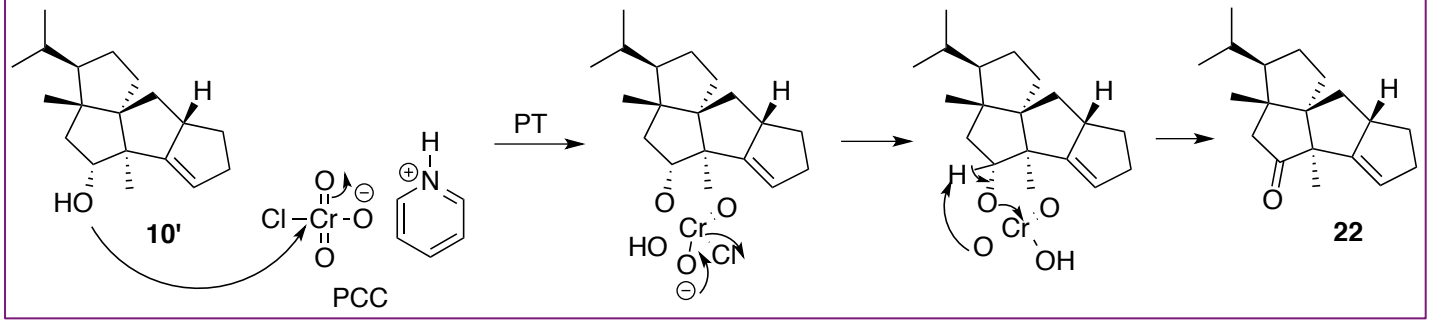
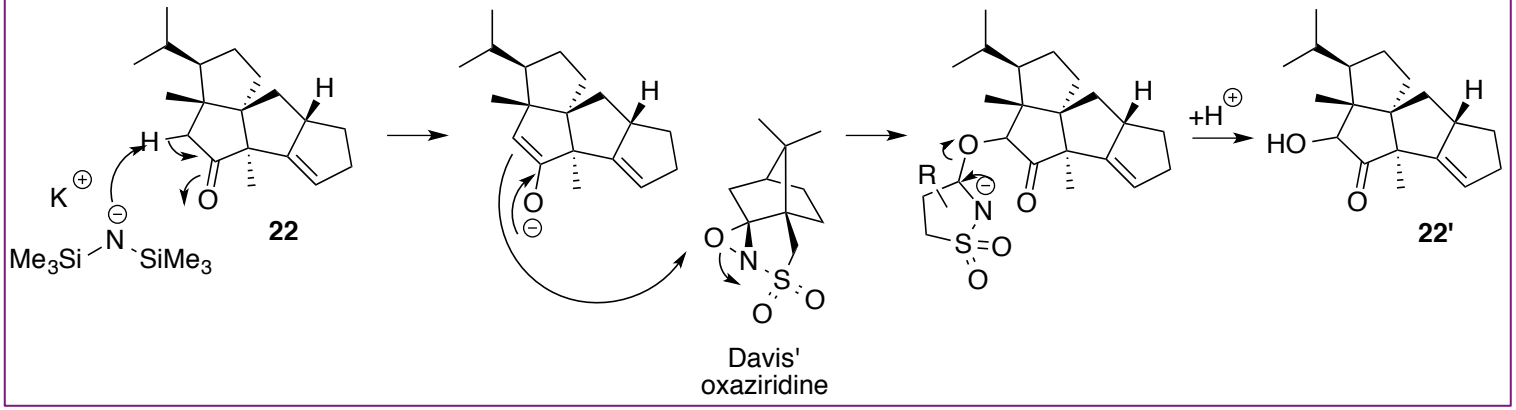
Mechanism m:
See mechanism b

Mechanism n: PCC oxidation

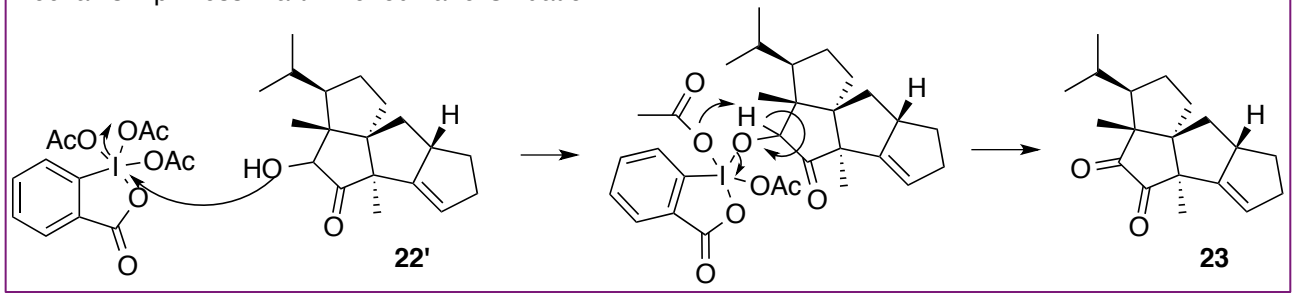


Mechanism o:

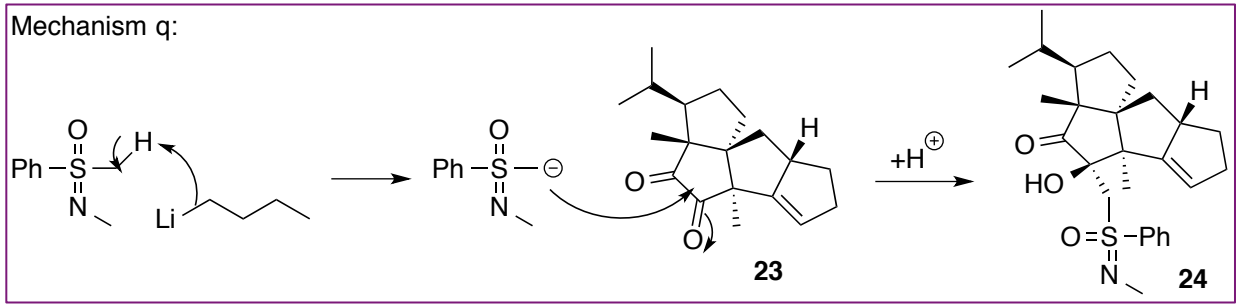


Total Synthesis of (–)-Crinipellin A

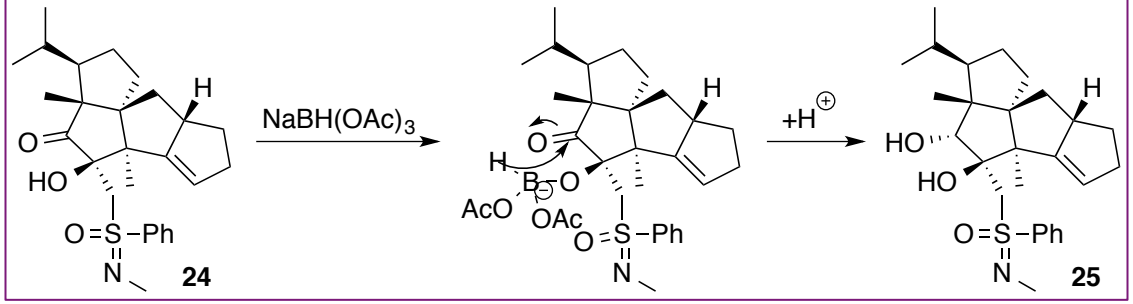
Mechanism p: Dess-Martin Periodinane Oxidation



Mechanism q:



Mechanism r: Hydroxyl-directedRreduction



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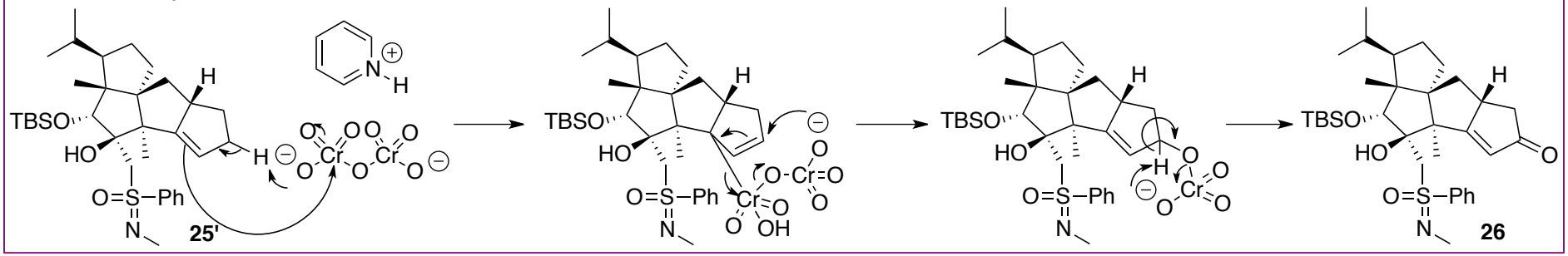
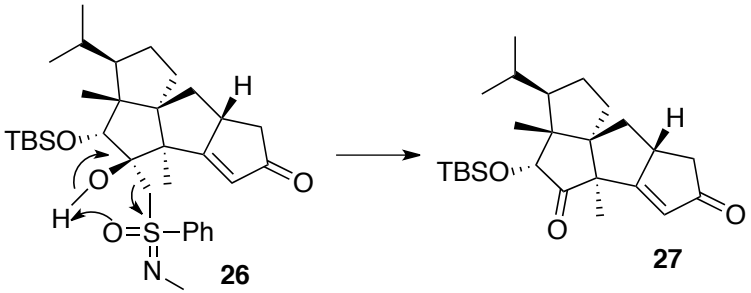
Mechanism s: TBS protection
See mechanism j

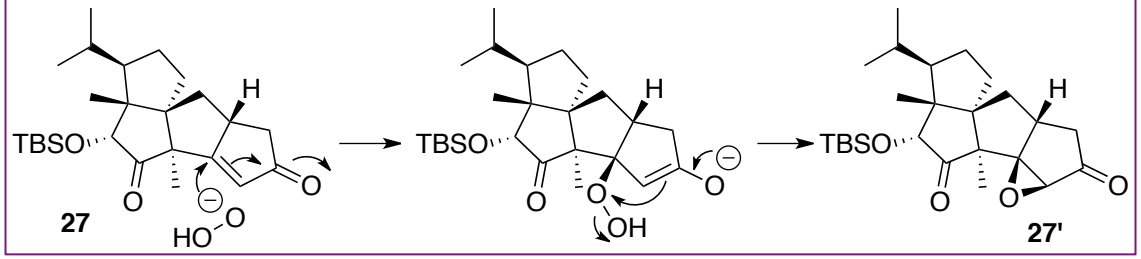
Mechanism t: Allylic oxidation



Mechanism u:



Mechanism v: Nucleophilic epoxidation



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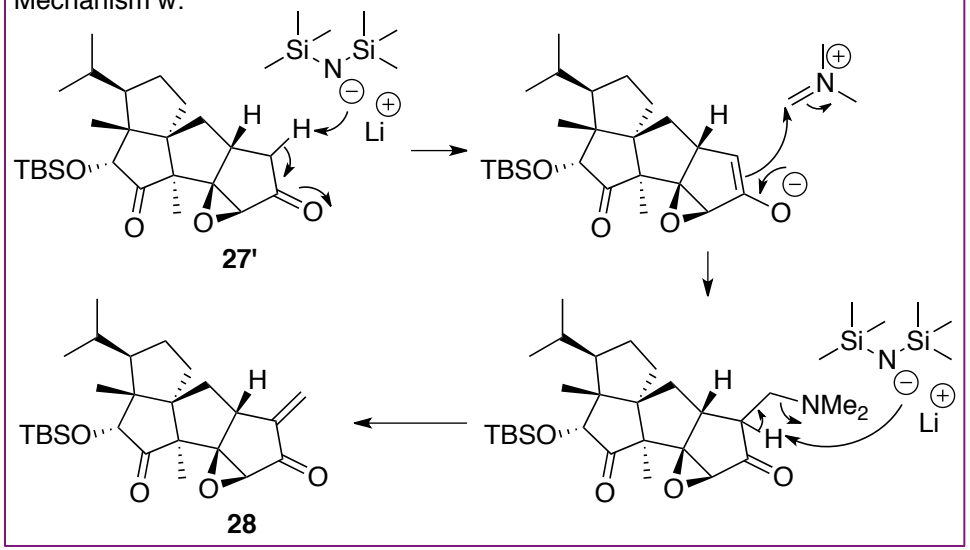
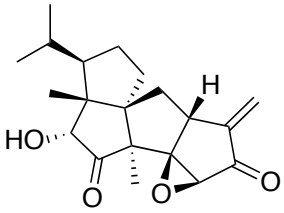
Mechanism w:



Mechanism x: TBAF deprotection
See mechanism b



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