Nineteen-Step Total Synthesis of (+)-Phorbol

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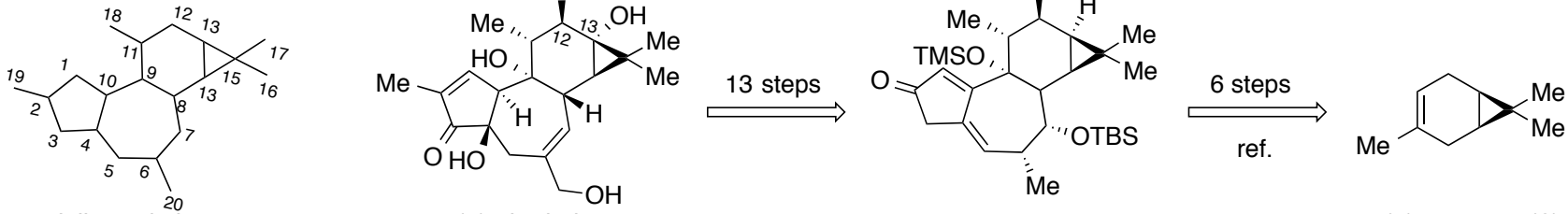
Introduction

Phorbol belongs to a class of natural products known as tigliane diterpenes, which have shown promise in medicinal applications such as immunomodulatory, anti-viral, and anti-cancer applications. Most notably in this class of compounds, phorbol 12-myristate 13-acetate is in phase II clinical trials for treatment of actue myeloid leukaemia. Structural analogs of phorbol have demonstrated anti-cancer activity, however synthetic access to this family of compounds remains limited. The authors sought to address the synthetic challenges posed by phorbol not by designing new synthetic methods, but rather through careful analysis and employing synthetic methods developed decades ago. The unusual placement of two oxygen atoms at carbons 12 and 13 provide a significant challenge for synthetic chemists which has stymied efforts spanning 40 years. Previous syntheses of phorbol have required 40-52 steps and none were enantioselective. The authors report a concise 19 step, enantiospecific total synthesis of **1** from readily available (+)-3-carene.

Retrosynthetic Analysis



ref. Jorgensen, L. et al. *Science* **2013**, 341, 878-882

Nature **2016,** *532* (7597), 90-93.

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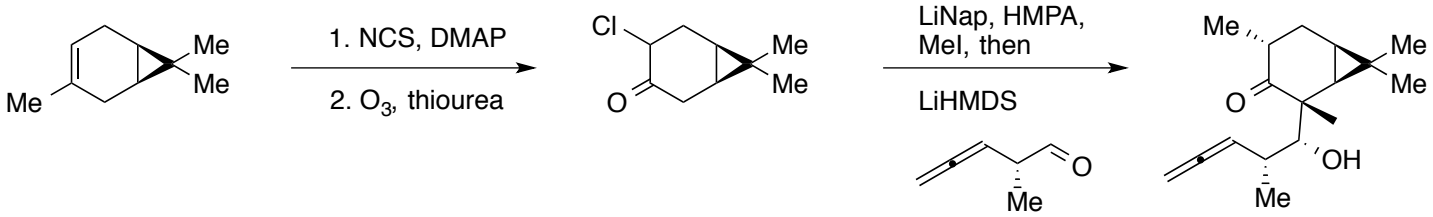
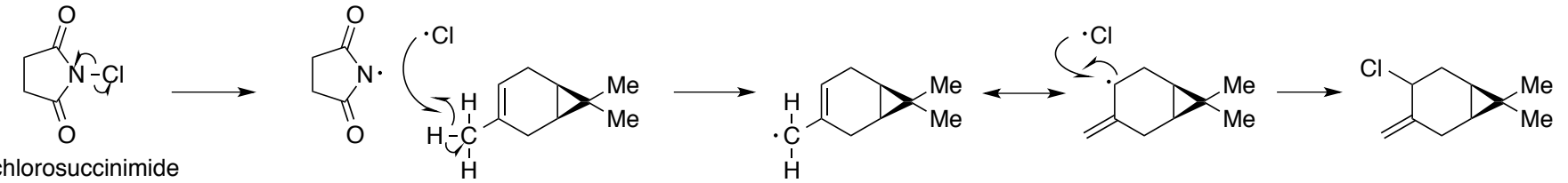
Synthesis of Allene Intermediate

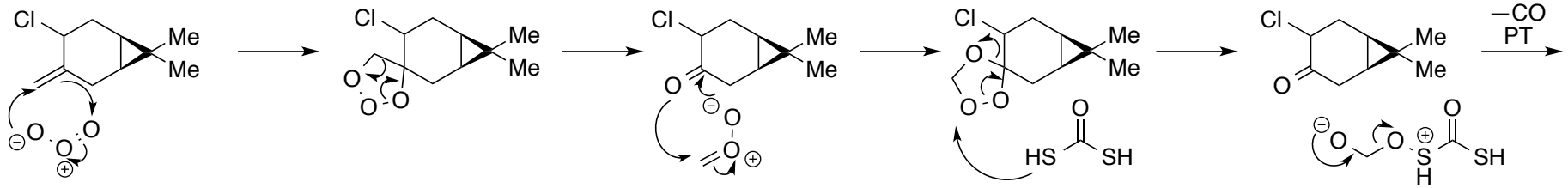


Allylic Chlorination

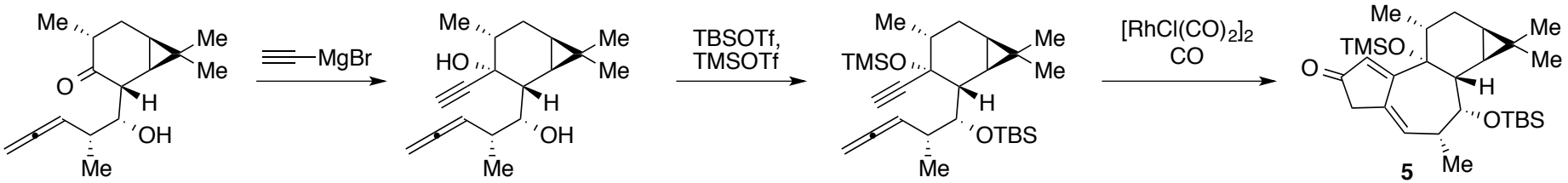


N-chlorosuccinimide

Ozonolysis

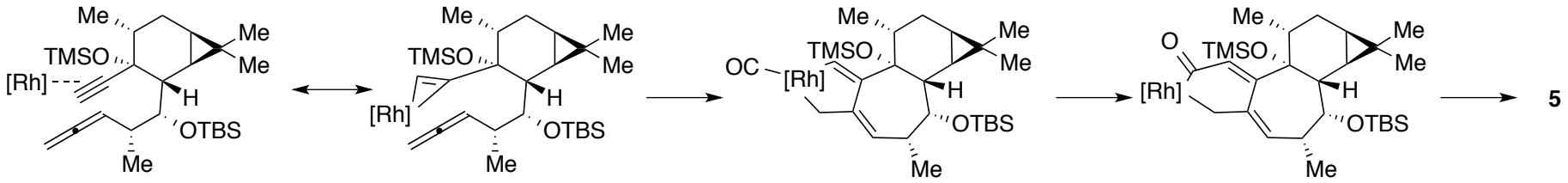


Synthesis of Intermediate 5

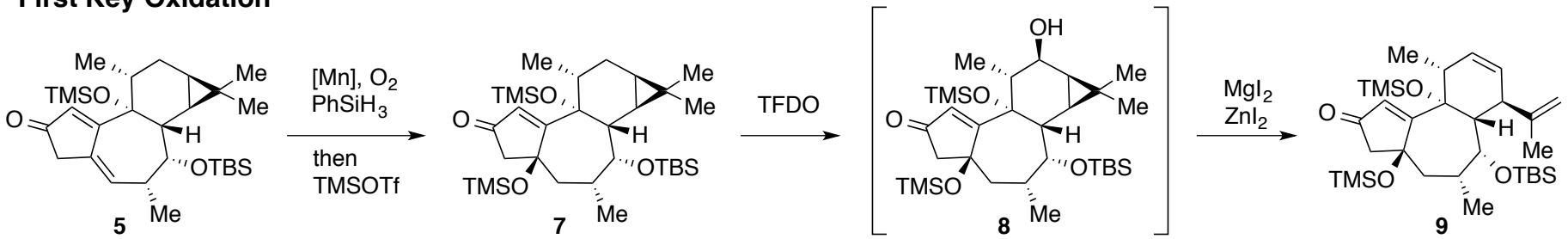


5

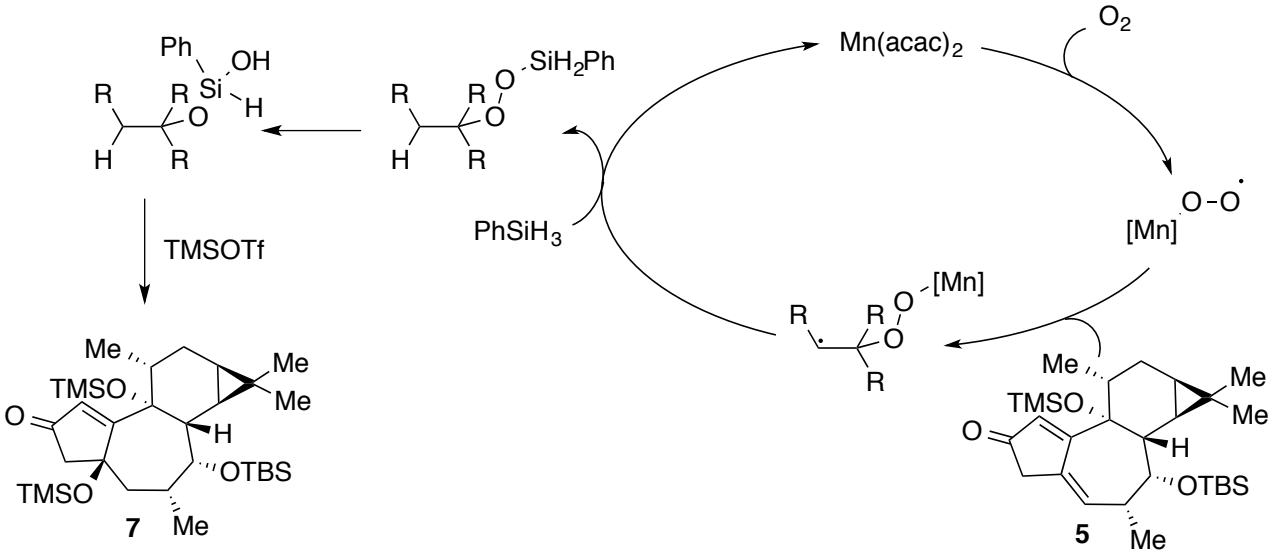
Rhodium Catalyzed Cyclization/Carbonylation



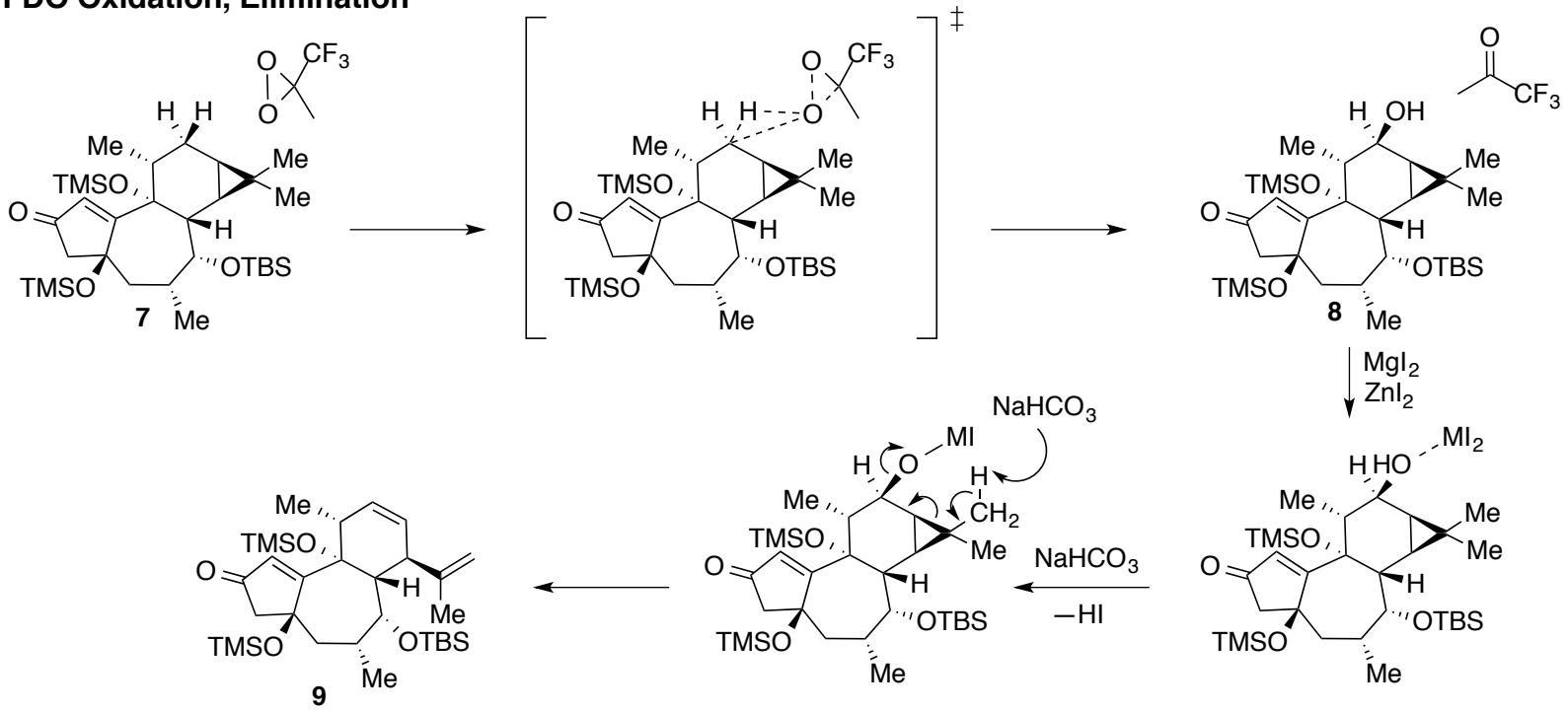
First Key Oxidation



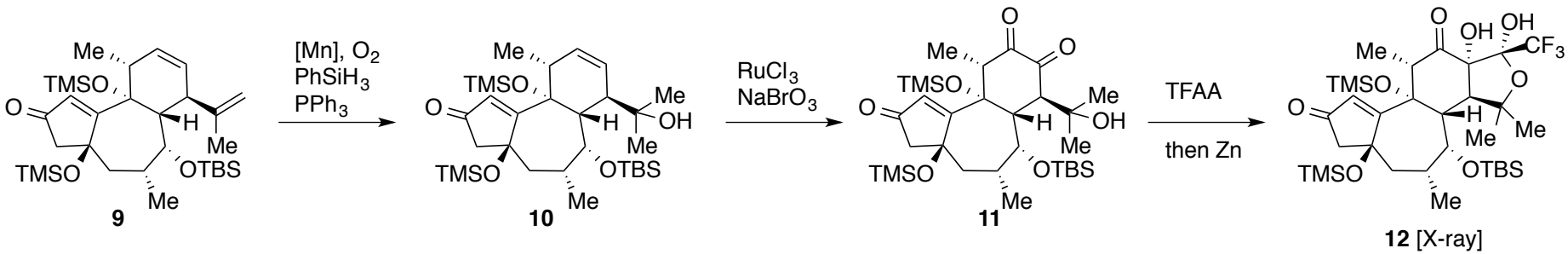
Mukaiyama Hydration



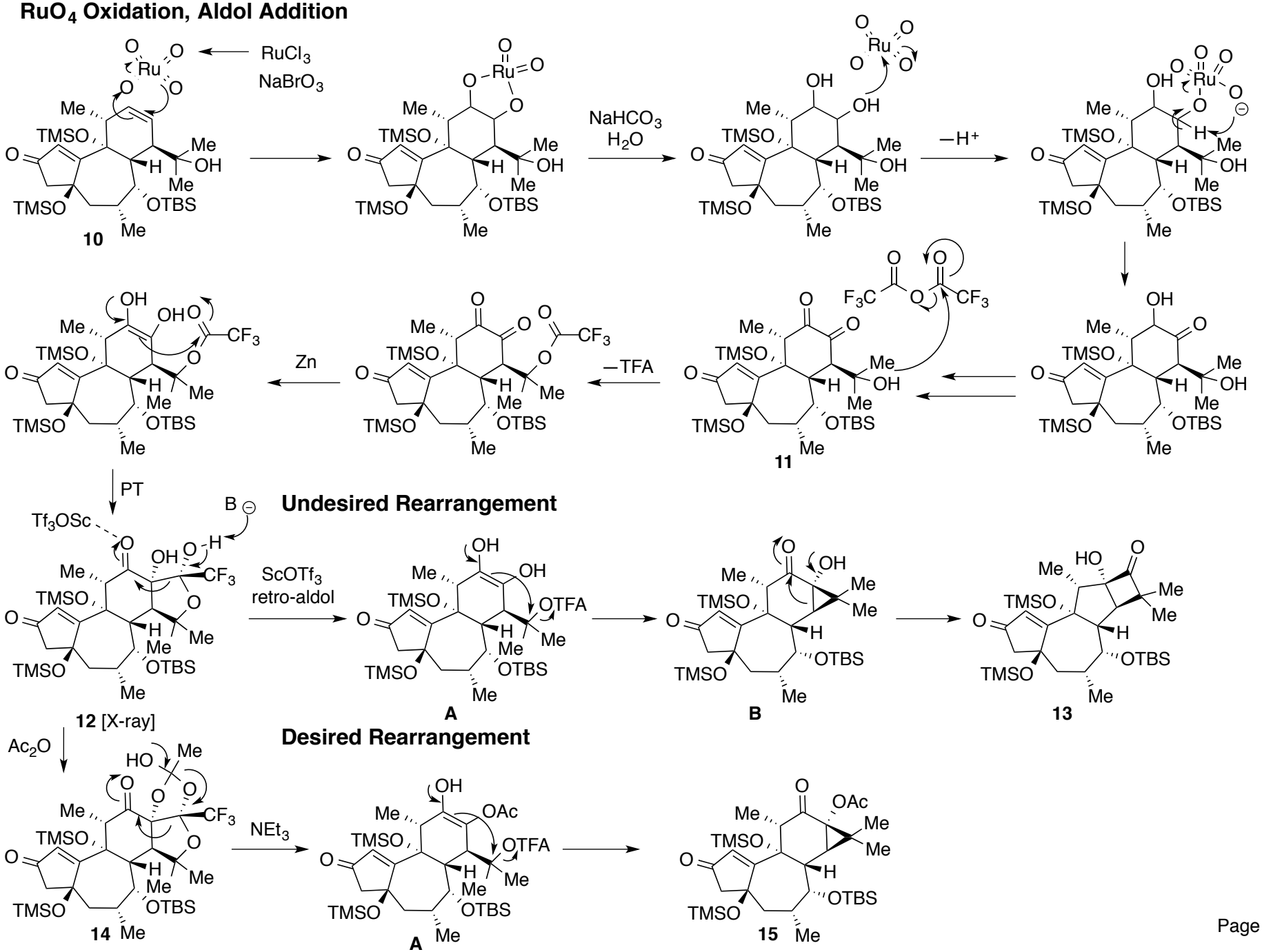
TFDO Oxidation, Elimination



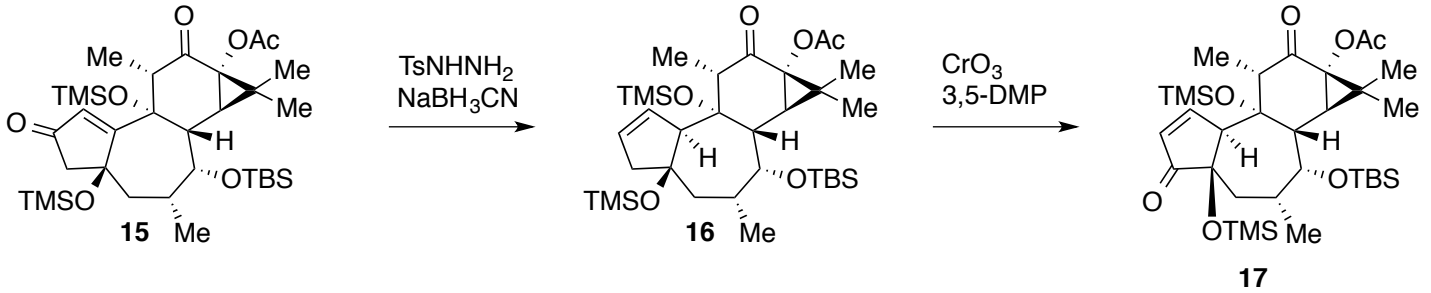
Second Key Oxidation



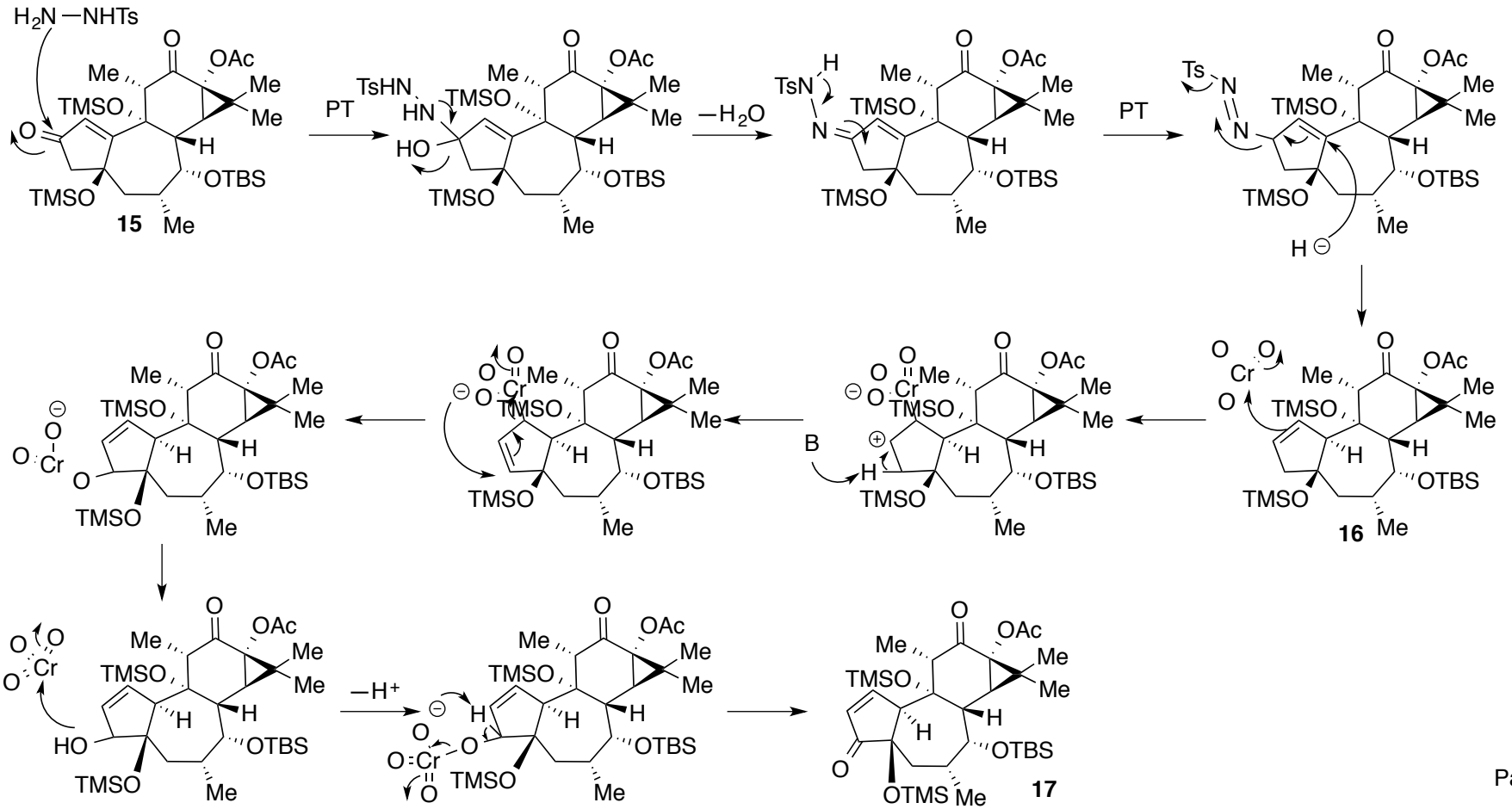
RuO_4 Oxidation, Aldol Addition



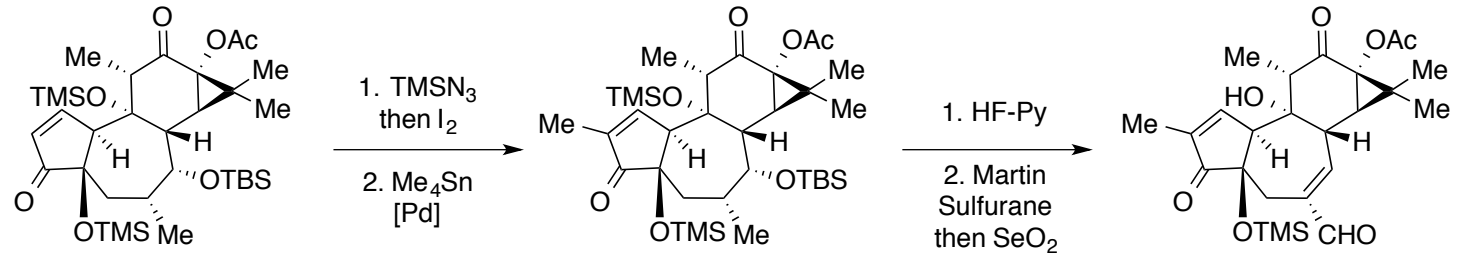
Cyclopentenone Rearrangement



Wolff-Kishner Reduction, Allylic Oxidation

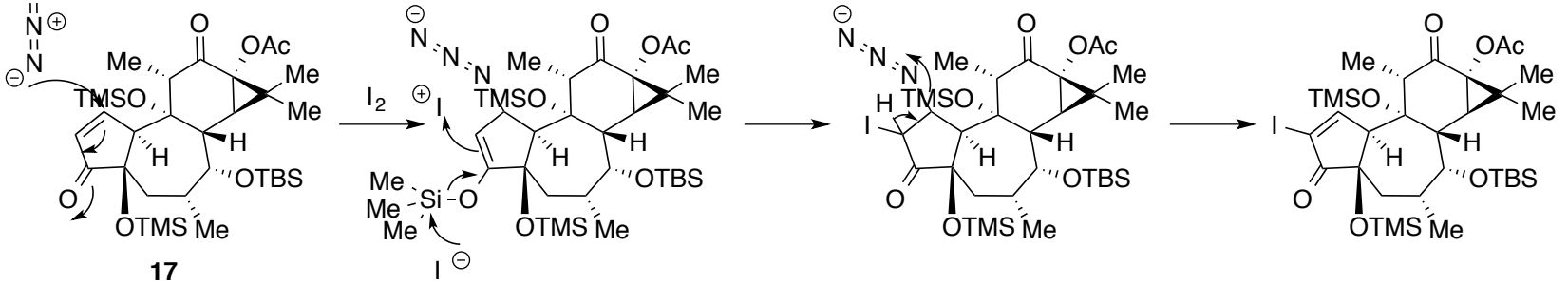


Synthesis of Intermediate 19



17 **18** **19**

alpha-iodo enone



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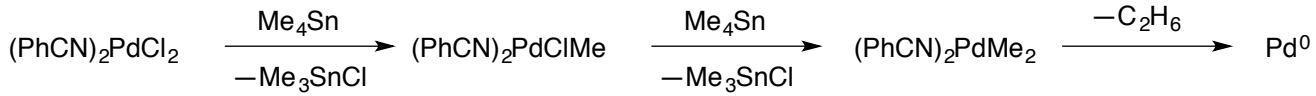
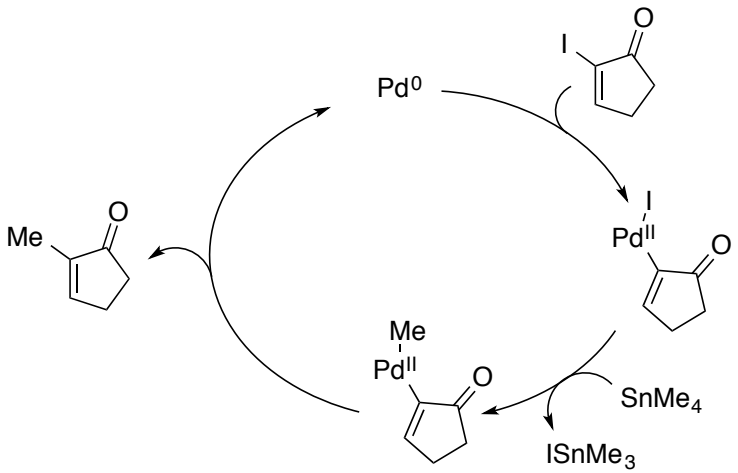
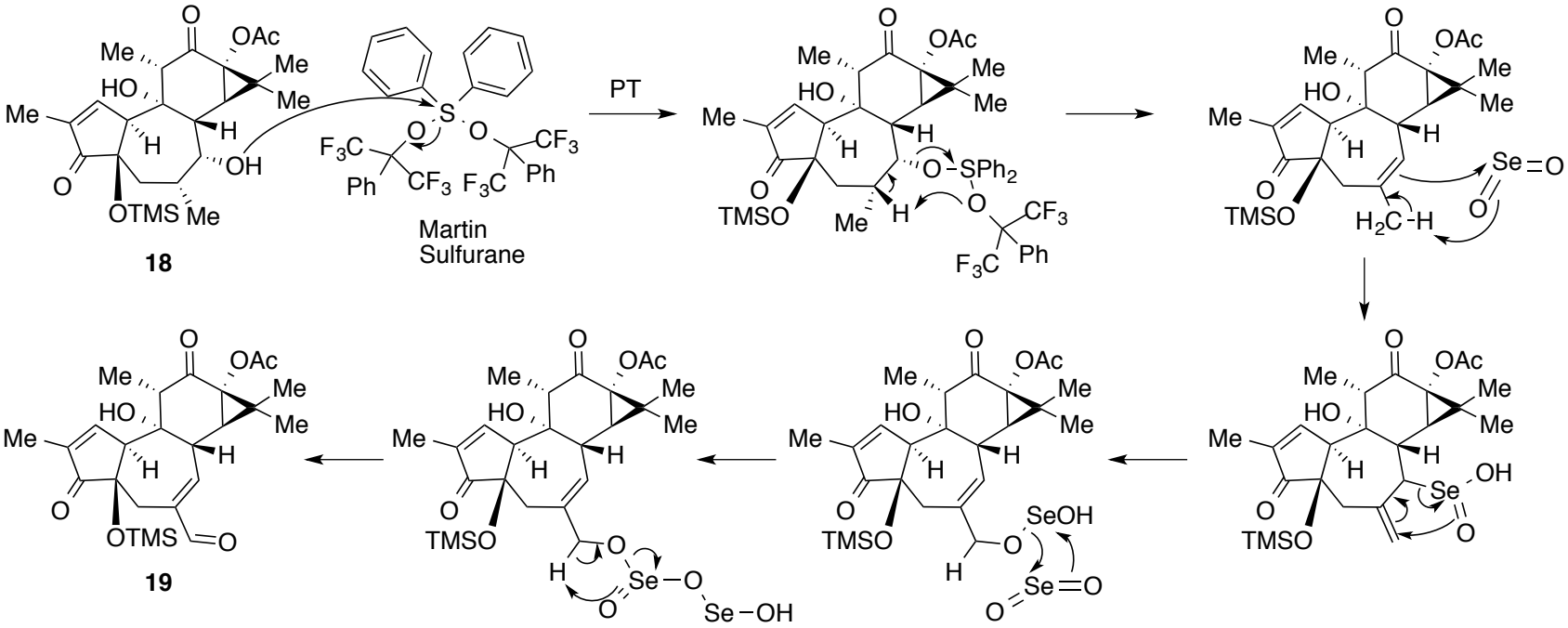
Cross Coupling





Dehydration, Allylic Oxidation



Finishing the Synthesis