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Total Synthesis of the Sesquiterpenoid Periconianone A Based on a Postulated Biogenesis

Raphael Liffert, Anthony Linden, and Karl Gademann*

Cameron McConnell
Professor S.-Y. Liu
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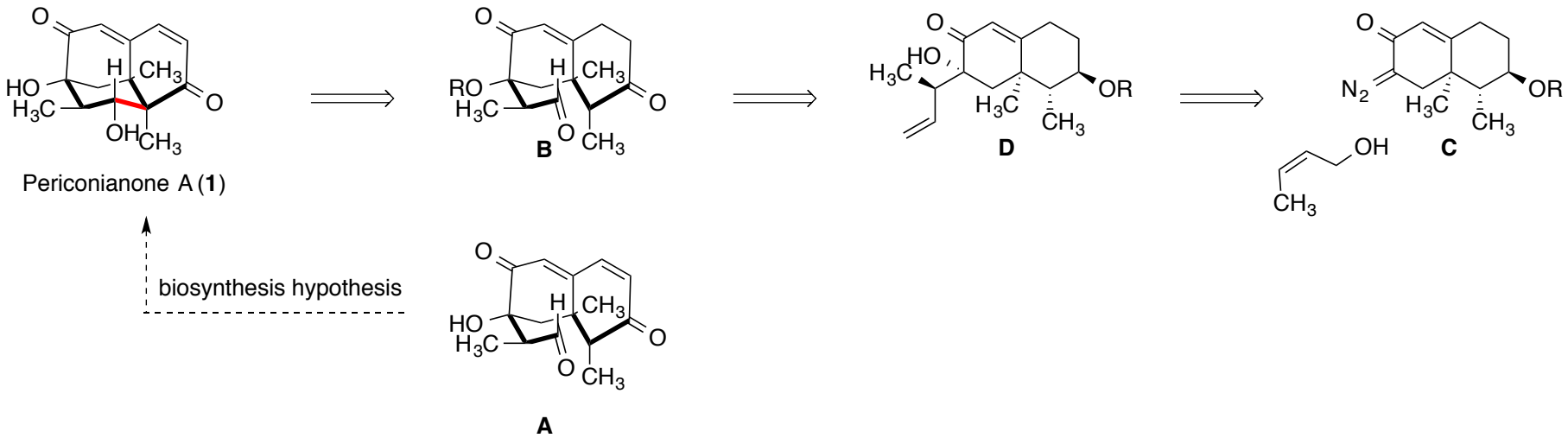
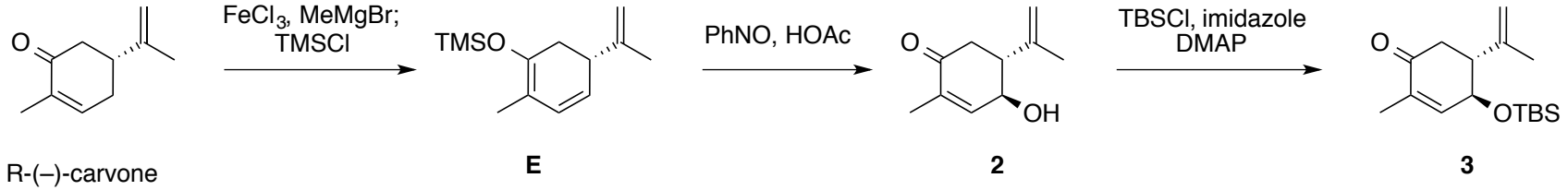
Introduction

Periconianone A is a complex tricarbocyclic sesquiterpenoid isolated from the endophytic fungus *Periconia sp*. In biology, polyene cyclizations and cationic rearrangements usually introduce structural diversity in terpenes at the initial cyclase phase. In this enantioselective total synthesis, the authors employ a late-stage aldol cyclization of the highly oxidized bicyclic eremophilane precursor B, which resembles a postulated aldol reaction from biological intermediate A. The synthesis also features a Rh mediated O-H insertion of a crotyl alcohol followed by a [3,3]-sigmatropic rearrangement to set up the unusual aldol reaction that constructs the 6/6/6 framework.

Synthetic Strategy

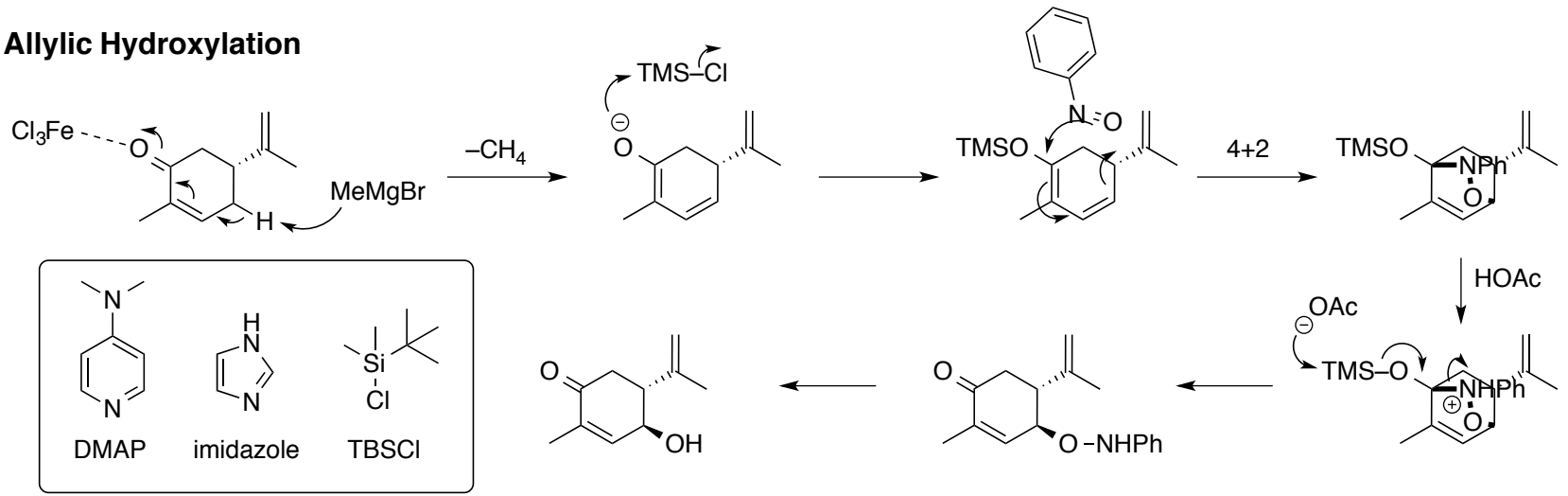


Oxygenation of Carvone

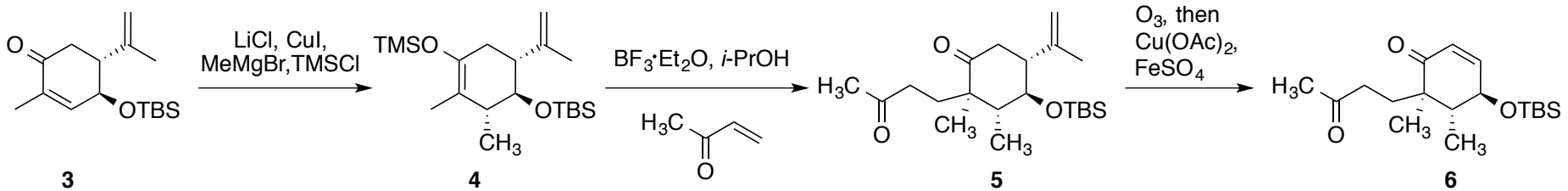


R-(–)-carvone **E** **2** **3**

Allylic Hydroxylation

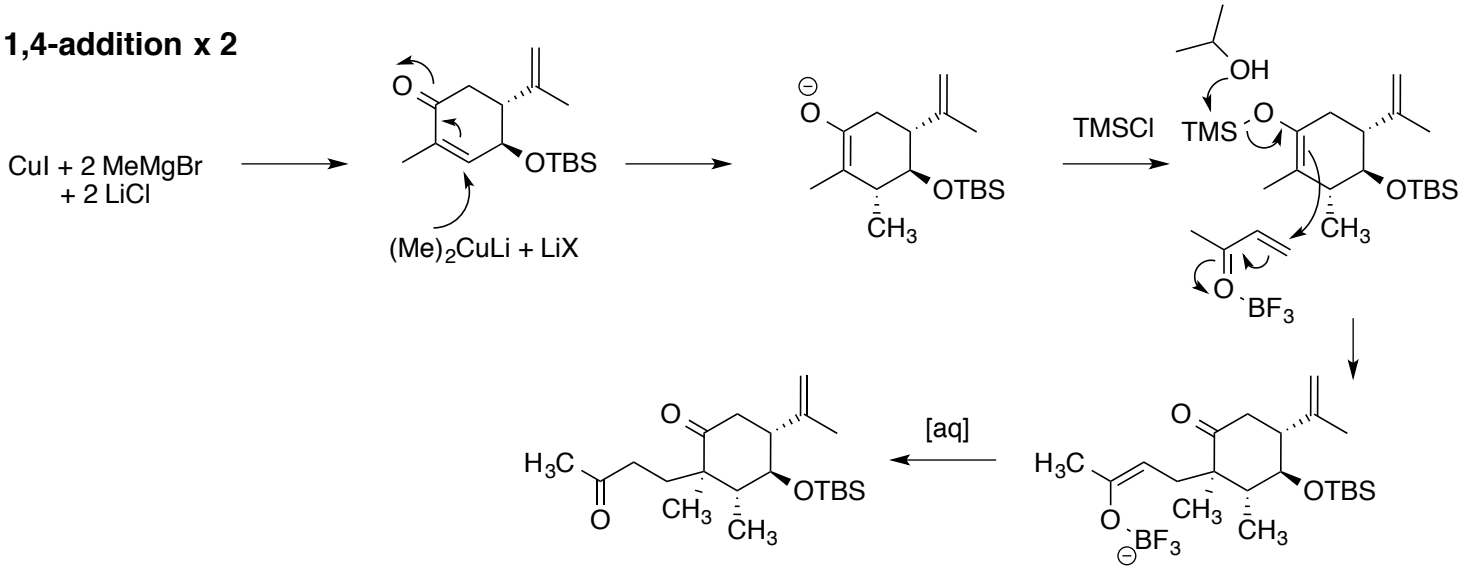


Preparation of Cyclohexenone 6

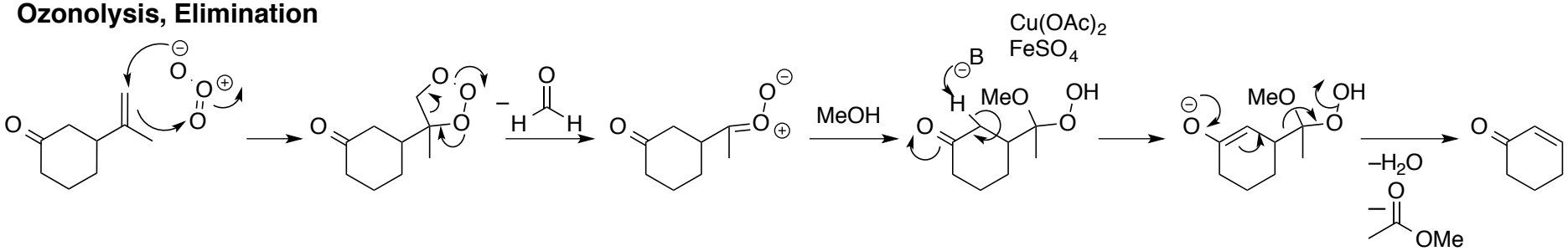


3 **4** dr >10:1 **5** dr >10:1 **6**

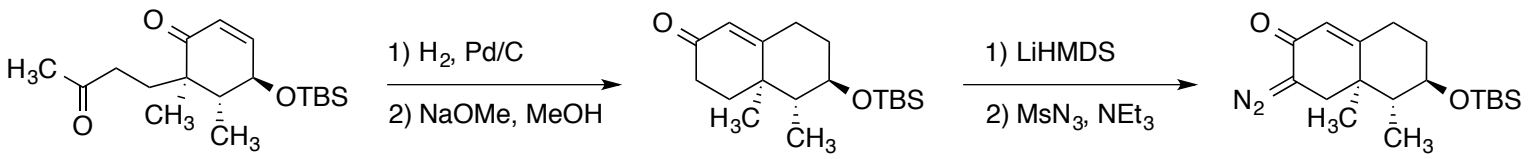
1,4-addition x 2



Ozonolysis, Elimination

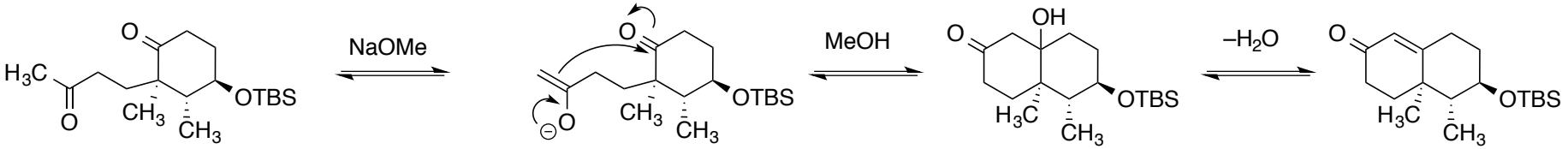


Preparation of Diazo Compound 8

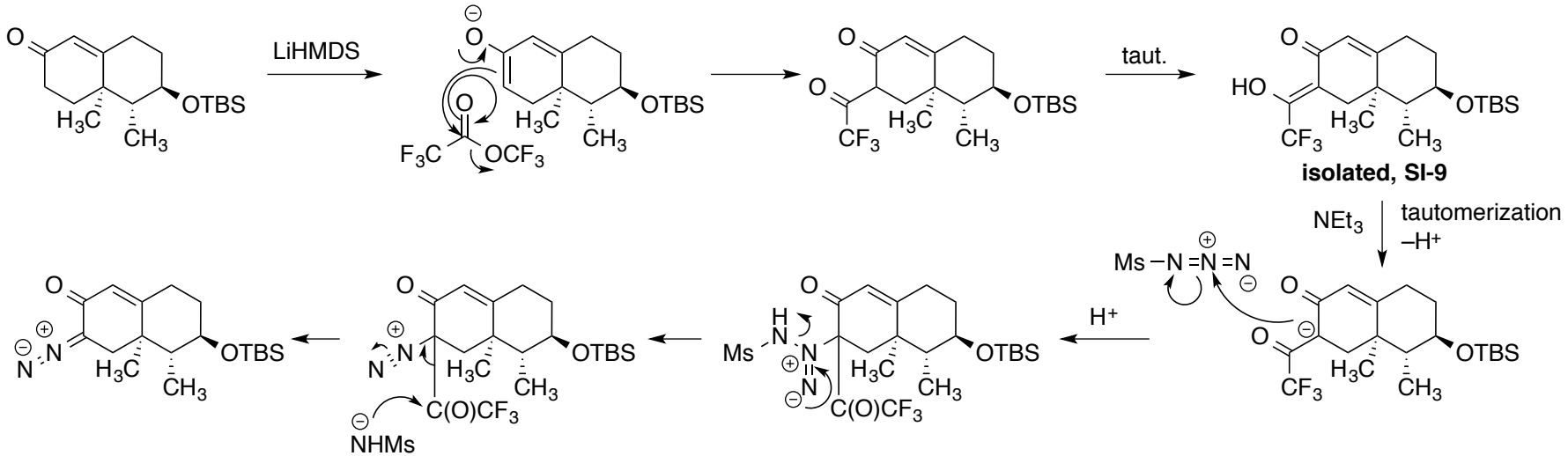


6 **7** **8**

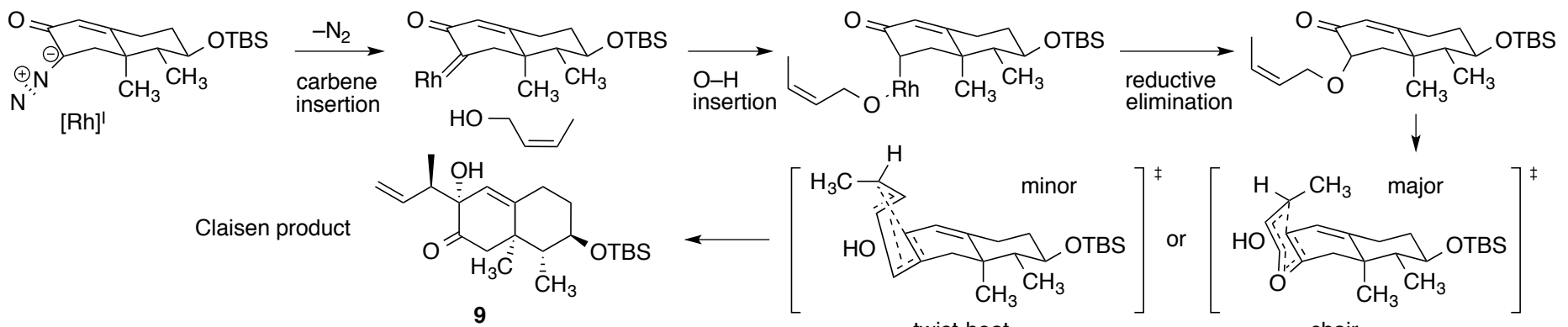
Robinson Annulation



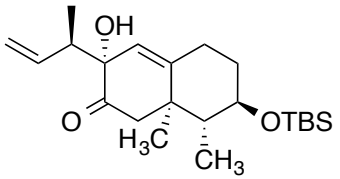
Diazo Formation



Rh-Mediated O-H Insertion, [3,3]-Sigmatropic Rearrangement (Claisen)

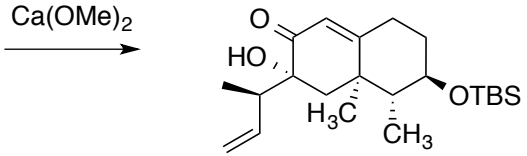


Alpha-Ketol Rearrangement



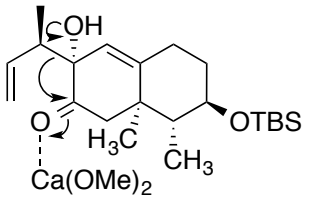
9

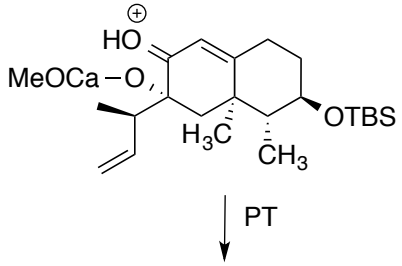
dr 3:1, major diastereomer shown



10

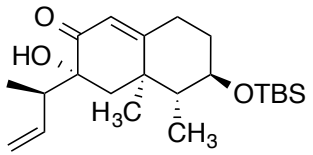
dr 14:1, after separation





10

Construction of the 6/6/6 Tricarbocyclic Framework



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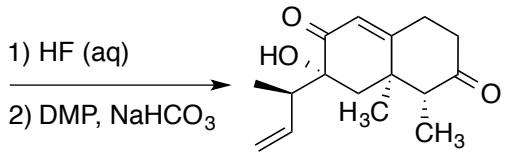

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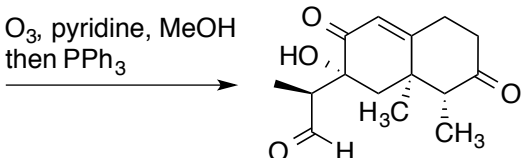
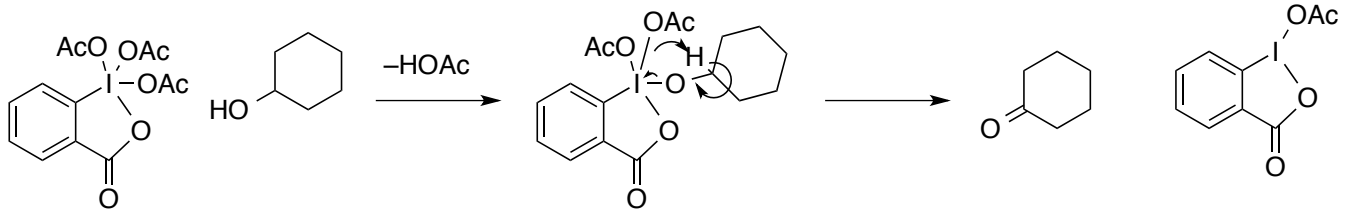
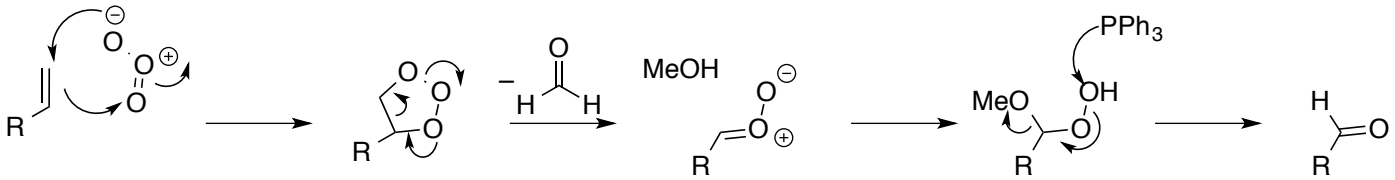


12

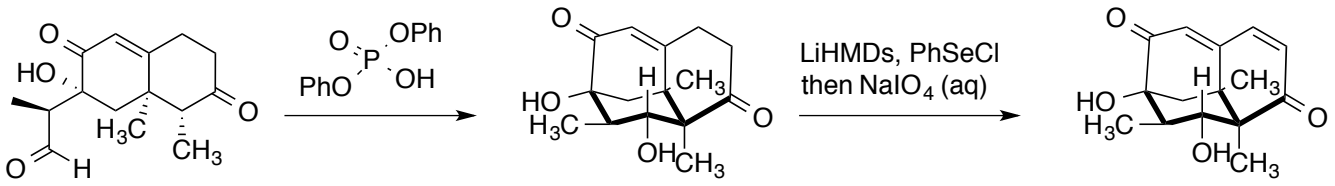
DMP Oxidation



Ozonoylsis/Criegee Fragmentation

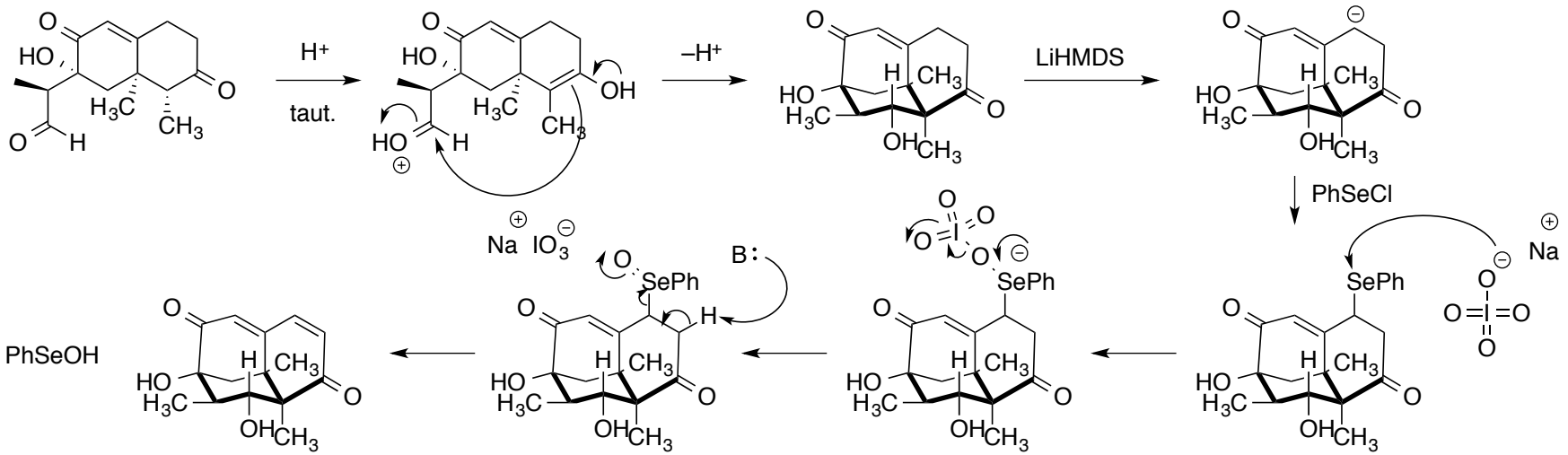


Construction of the 6/6/6 Tricarbocyclic Framework cont.



12 → **13** dr >10:1 → Periconianone A (**1**)

Aldol Reaction and Allylic Oxidation



Conclusion

The target compound, Periconianone A, was prepared in an enantioselective fashion in 14 steps from Carvone. The synthesis features a biomimetic, late-stage aldol reaction to construct the 6/6/6 carbocyclic framework. The synthesis also features a Rh mediated O-H insertion followed by a spontaneous Claisen rearrangement and an alpha-ketol rearrangement to install the C7 carbinol, a challenge heretofore not addressed for eremophilane-type natural products.