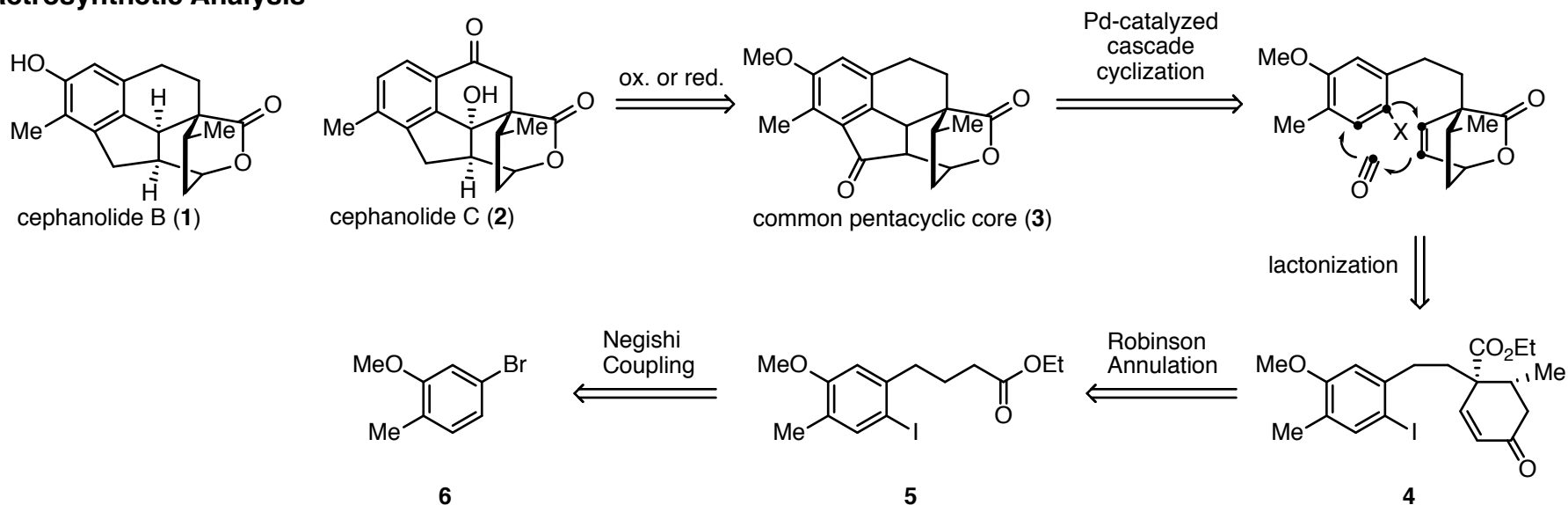


Lun Xu, Chao Wang, Ziwei Gao, and Yu-Ming Zhao*

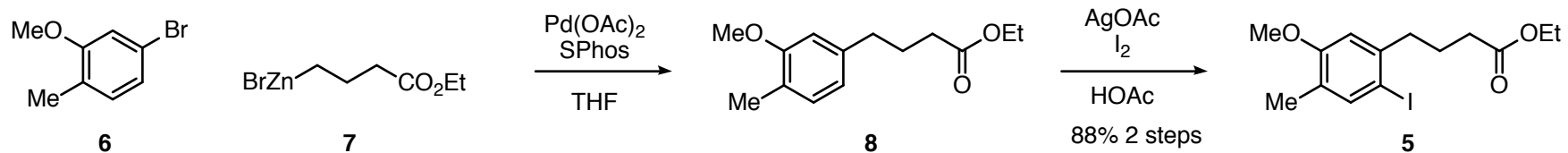
Introduction

The first total synthesis of Cephanolides B and C is reported. The Cephanolide norditerpenoids belong to a larger family of structurally diverse natural products produced by the plants of the *Cephalotaxaceae* family. Cephanolide diterpenoids have been shown to demonstrate potent antitumor activity. They feature a common pentacyclic core which includes a *cis*-fused tricyclobycle, a cyclohexane ring bearing 5 or 6 contiguous stereogenic centers, and a bridging lactone ring. These challenging yet intriguing structural features combined with the biological activity of the Cephanolide diterpenoids have led to the the total synthesis of several other natural products from this family. In this paper, the authors report the first total synthesis of Cephanolides B and C through a common pentacyclic core which was accessed via a Heck-type/carbonylative C–H activation cascade.

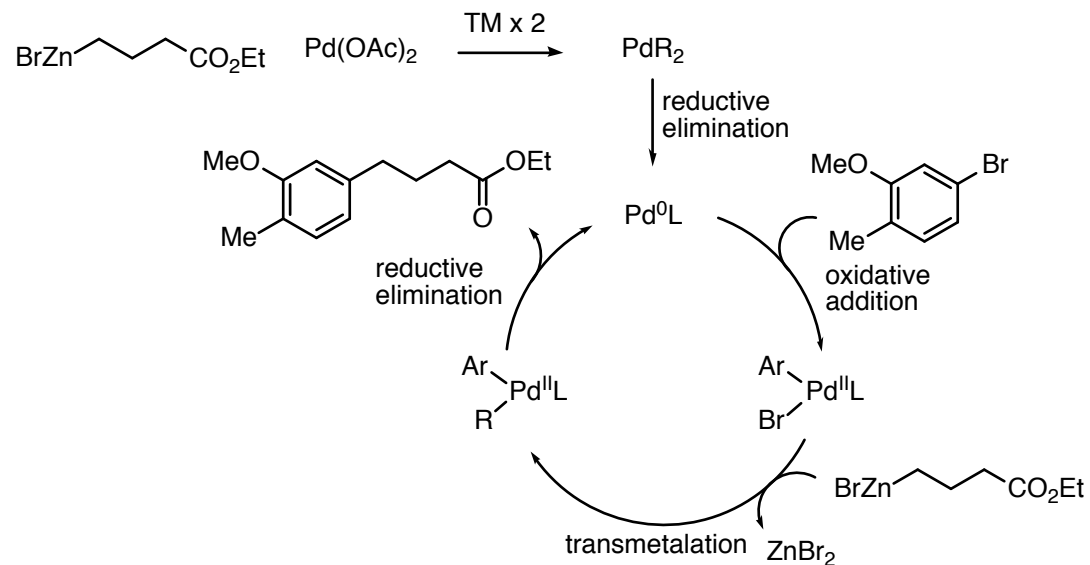
Retrosynthetic Analysis



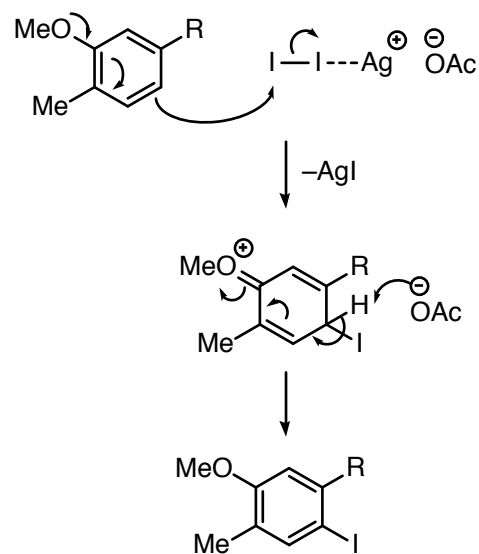
Synthesis of 5



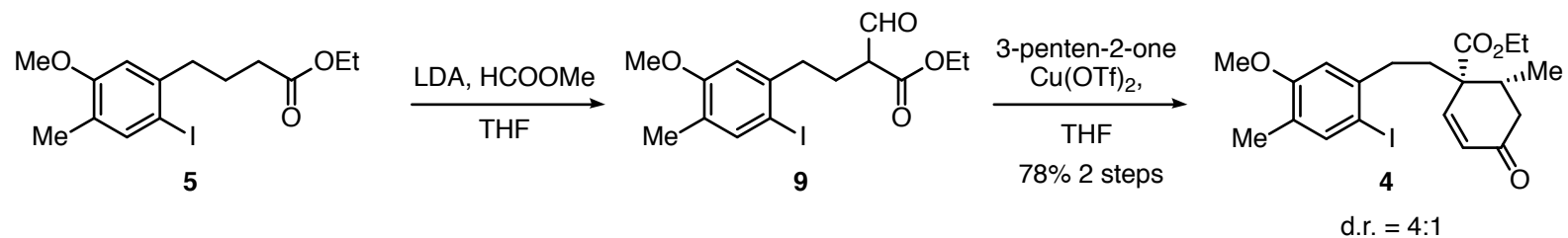
Negishi Coupling



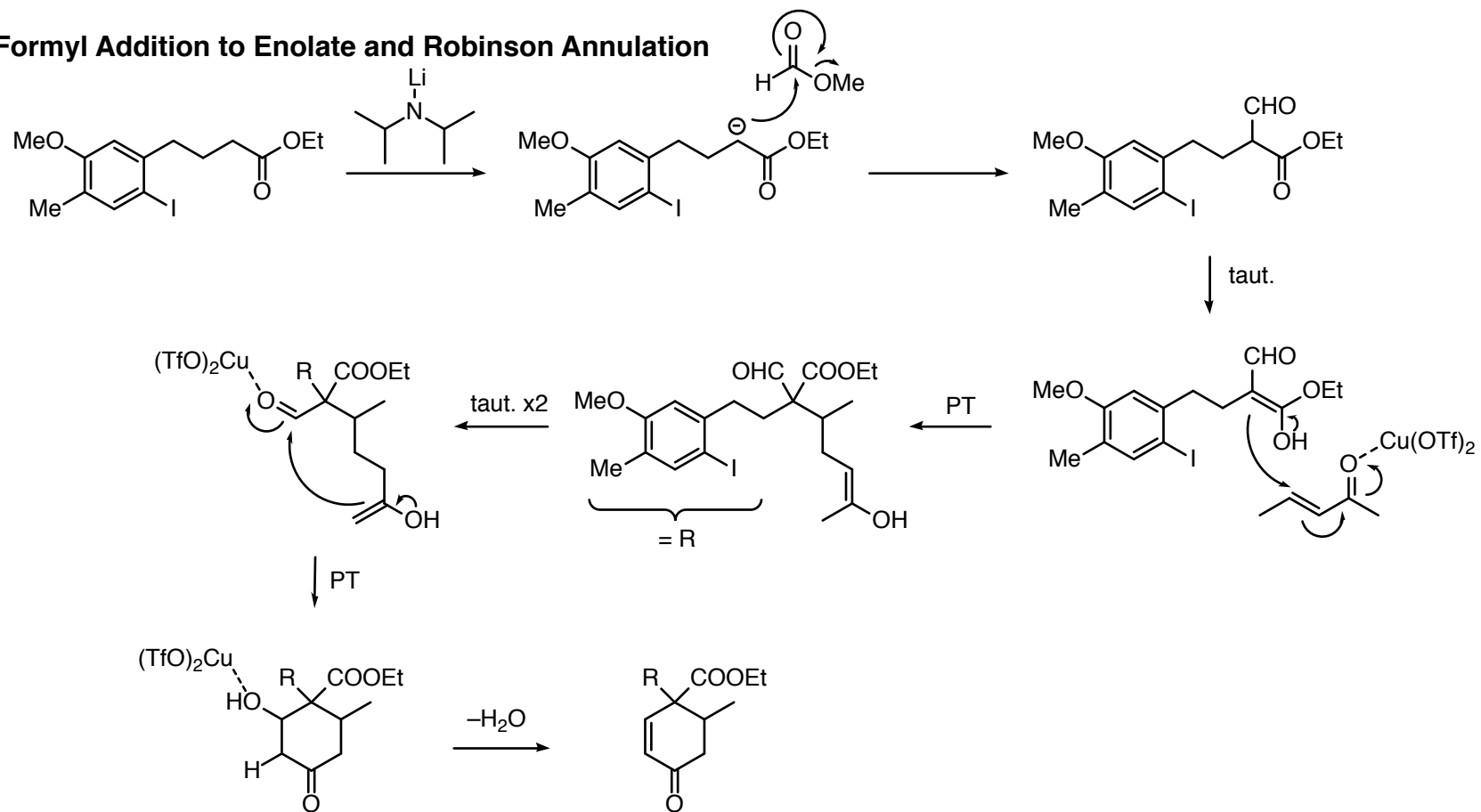
Electrophilic Aromatic Substitution



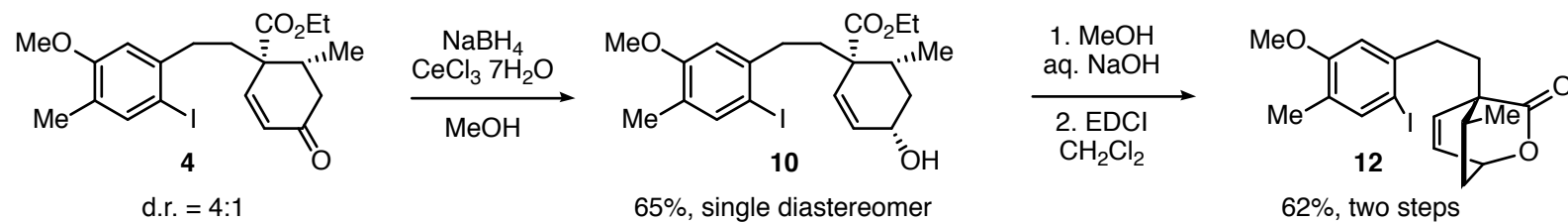
Synthesis of Cyclohexenone 4



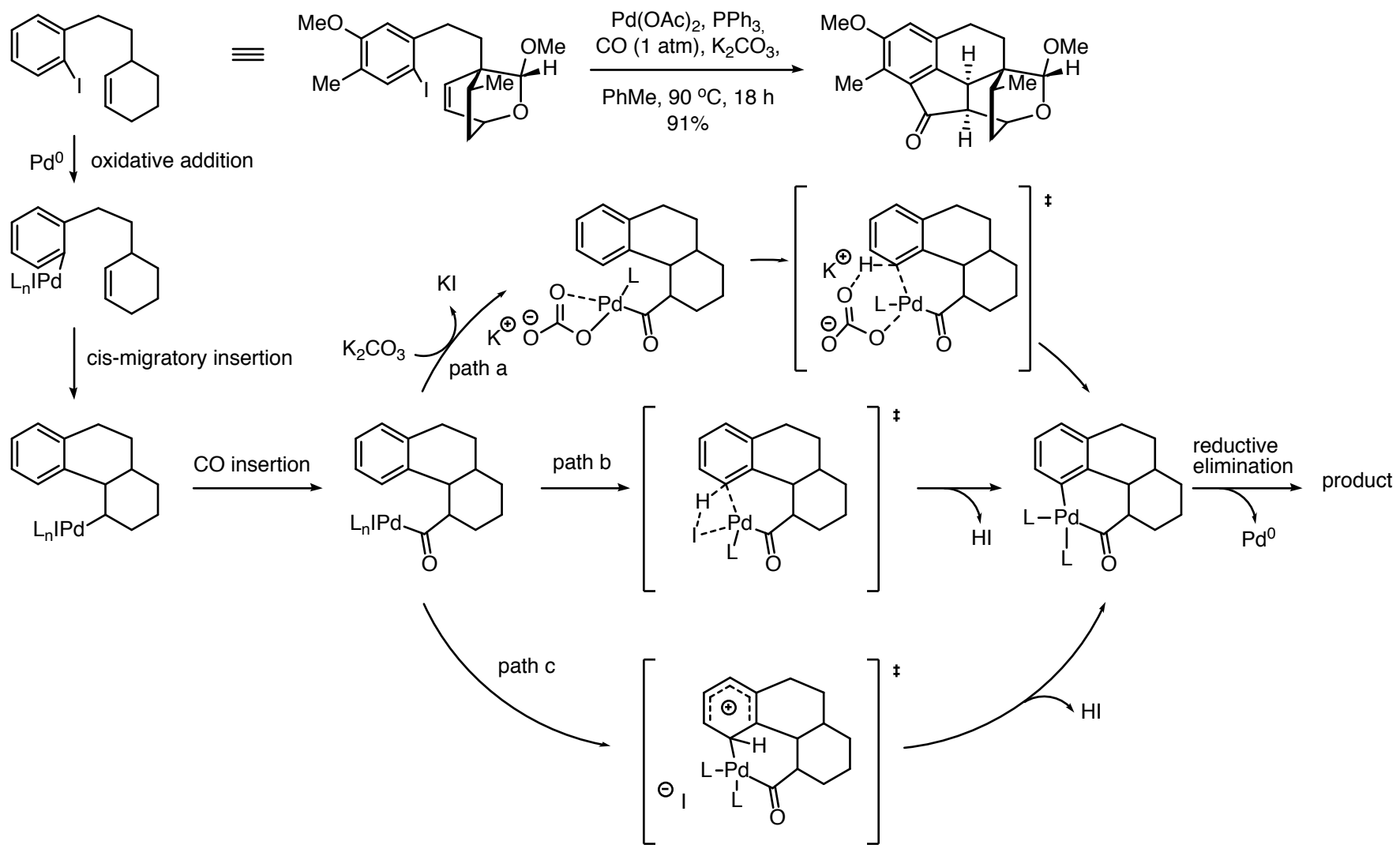
Formyl Addition to Enolate and Robinson Annulation



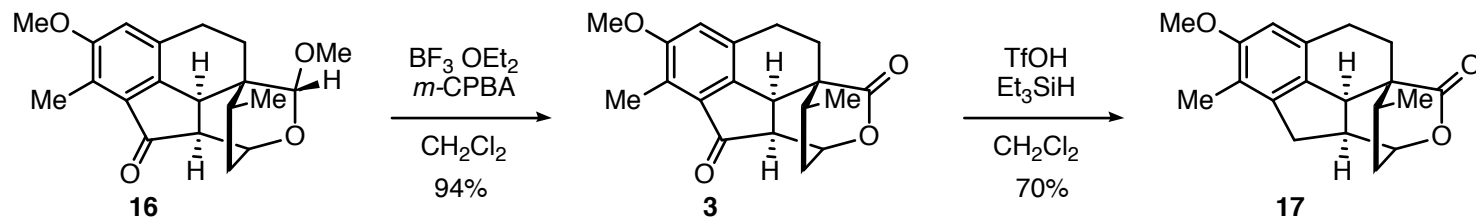
Formation of Lactone 12



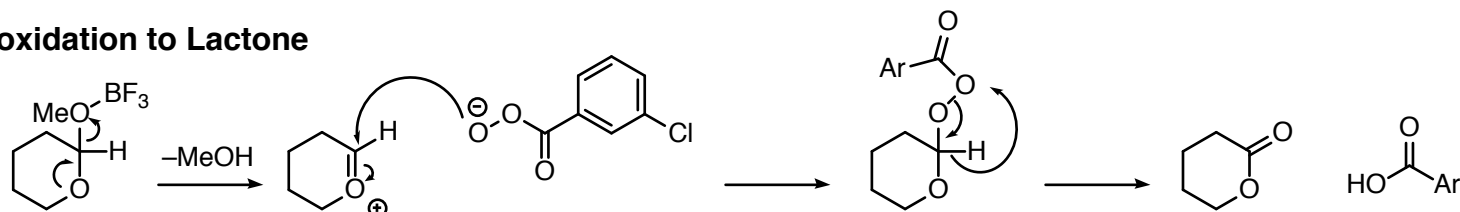
Palladium-Catalyzed Cascade Annulation



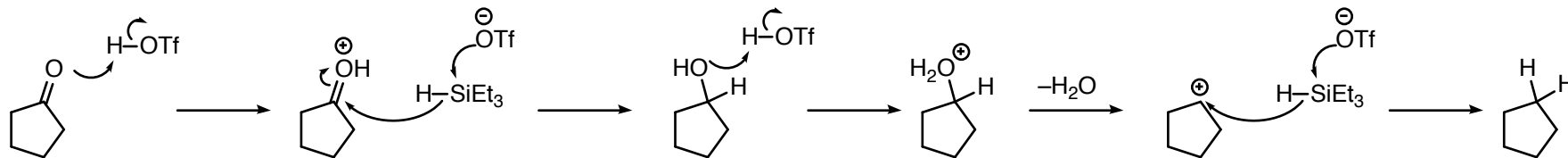
Preparation of Common Pentacyclic Core



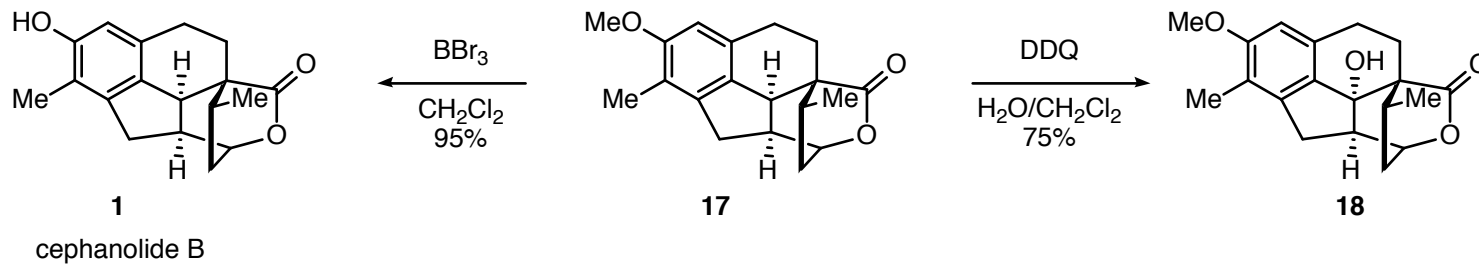
Re-oxidation to Lactone



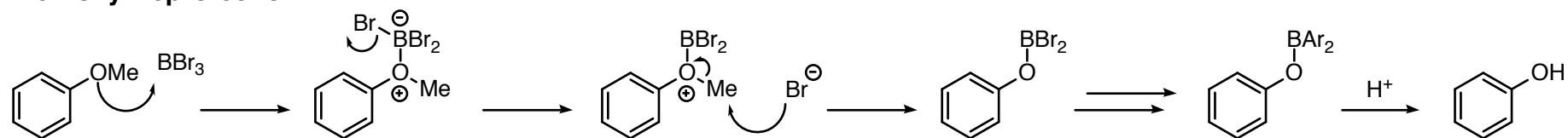
Reduction of Benzylic Ketone



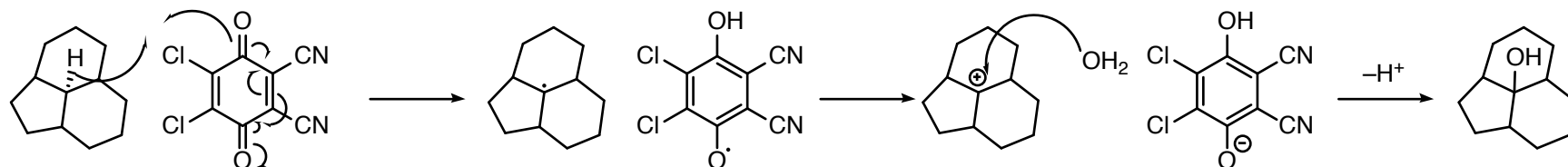
Divergence from Common Intermediate



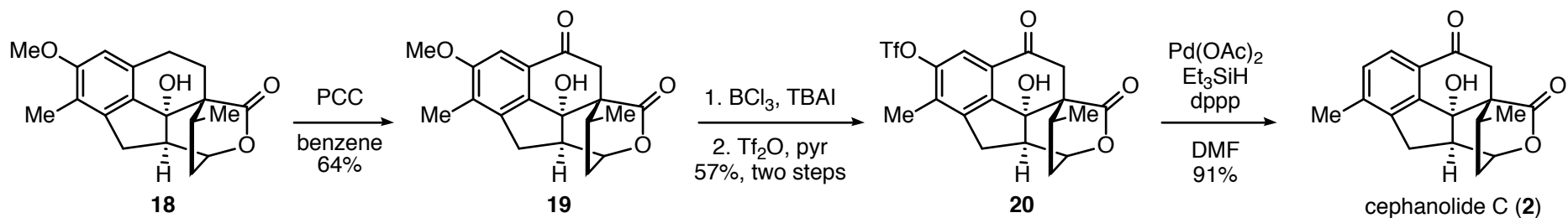
Methoxy Deprotection



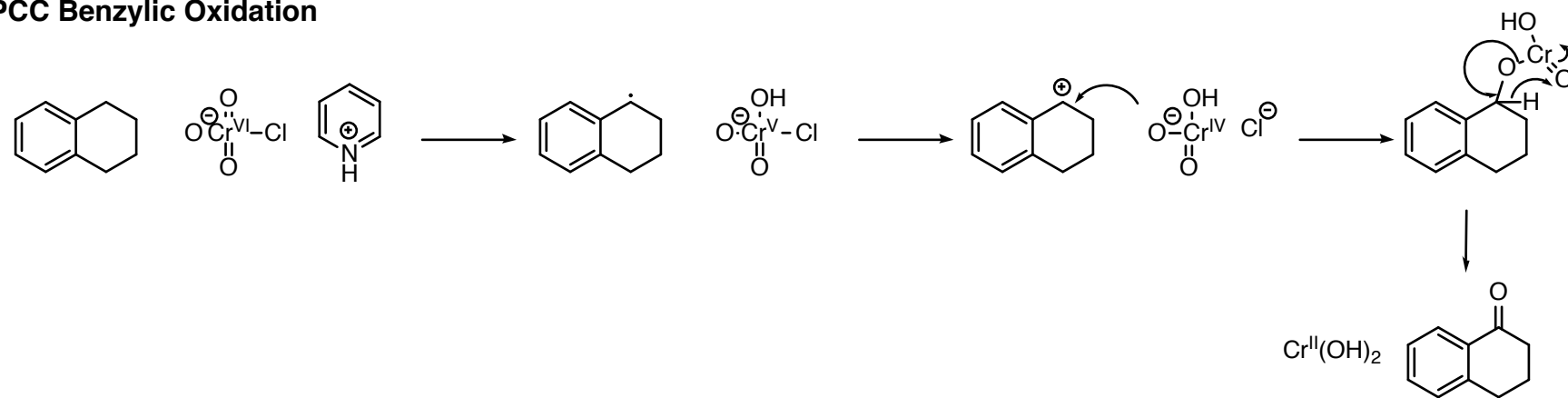
DDQ Oxidation



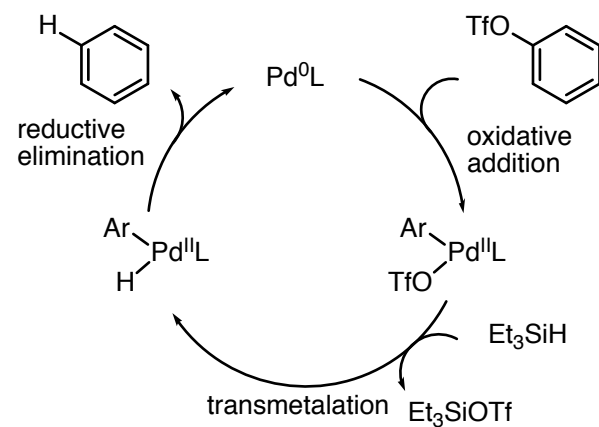
Completing the Synthesis of Cephanolide C



PCC Benzylic Oxidation



Pd-Catalyzed De-oxygenation



Conclusion

The first syntheses of the cephalotaxus diterpenoids cephanolide B and cephanolide C were accomplished in a longest linear sequence of 13 and 17 steps, respectively. A novel Pd-catalyzed cascade annulation reaction enabled the construction of a common pentacyclic core that can be elaborated into multiple cephalotane-type diterpenoids. The synthesis also featured two selective, late-stage, sp³ C-H oxidation reactions in order to prepare cephanolide C.