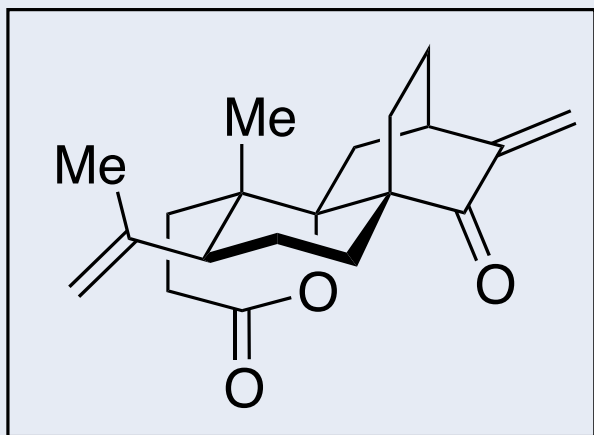


Total Synthesis of (+)- Crotoougoudin

Simon Breitler and Erick M. Carreira
ETHZ, Switzerland

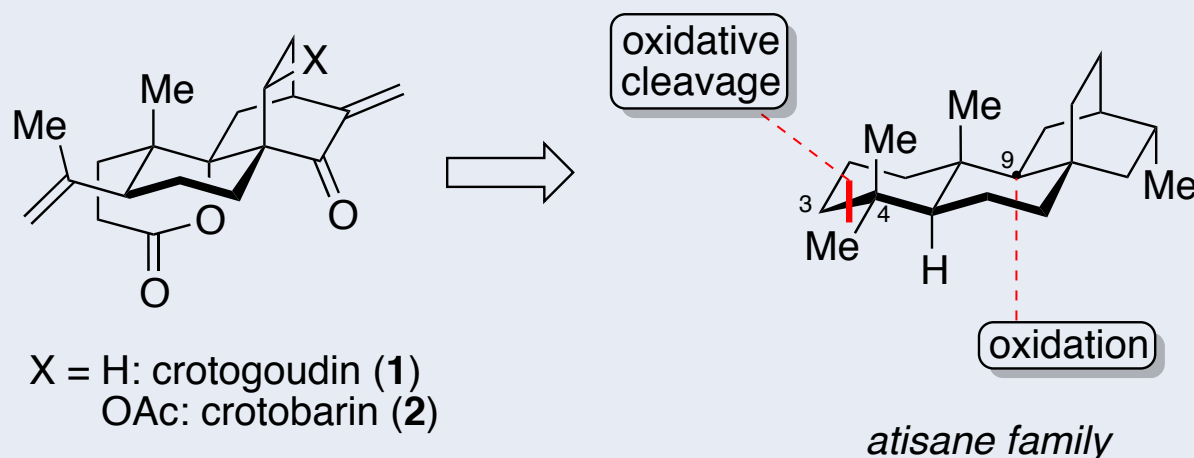
Angew. Chem. Int. Ed. **2013**, 52, 1-5.



Angewandte
International Edition
Chemie

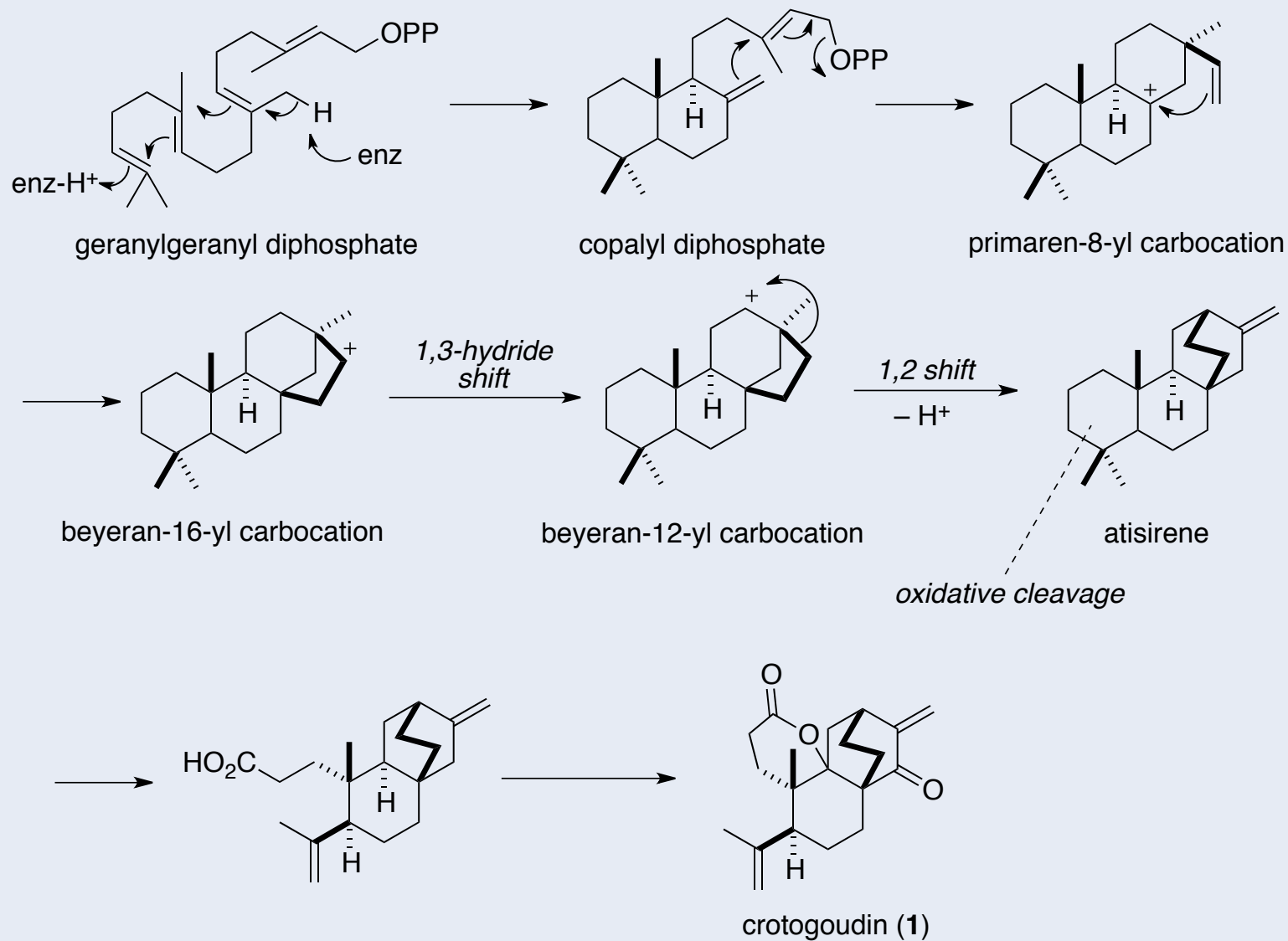
Introduction – Crotogoudin

- Isolated in 2010 by a Madagascan-French research group
- Two closely related cytotoxic diterpenes were isolated, **crotooudin 1** and **crotoouarin 2**
- Both **1** and **2** belongs to the rare 3,4-seco atisane family of diterpenoids

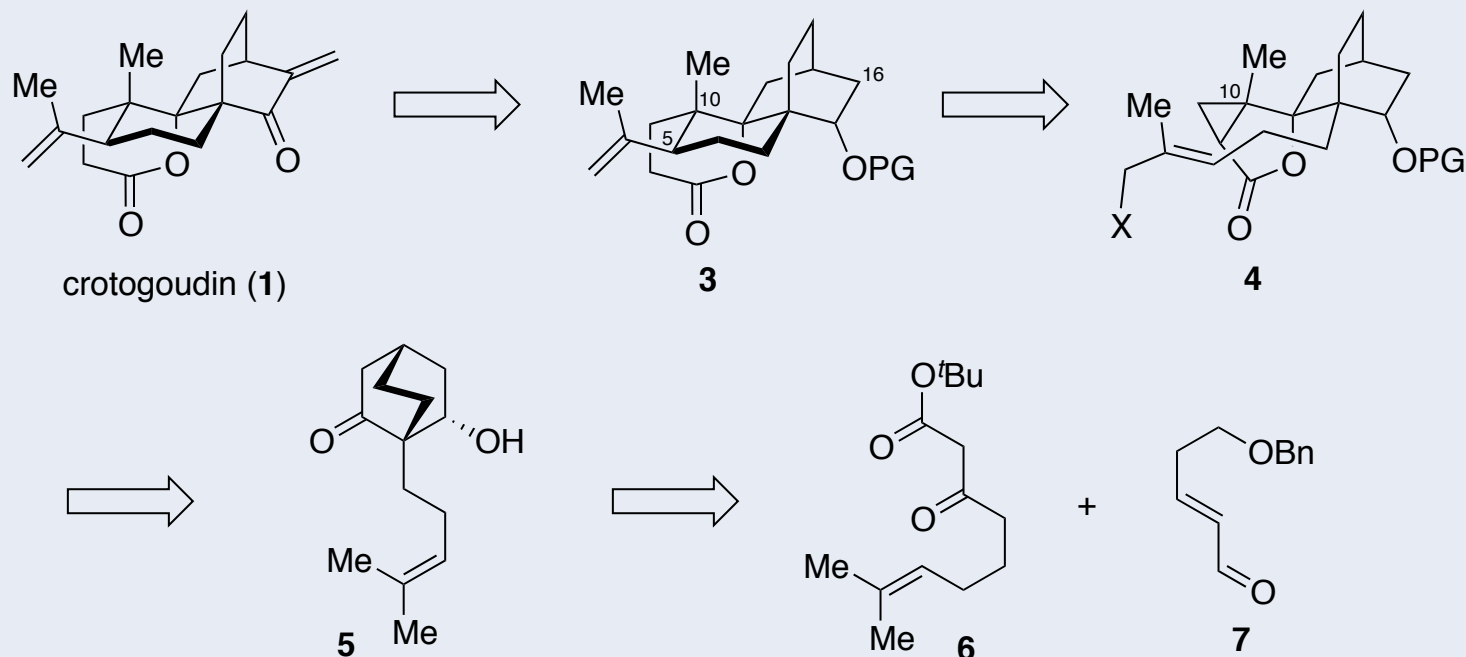


- Novel **diterpenes (C₂₀)** contains a polycyclic ring system with **four contiguous stereocenters**, where a six-membered ring is fused to a **bicyclo[2.2.2]octane** subunit

Proposed Biosynthesis

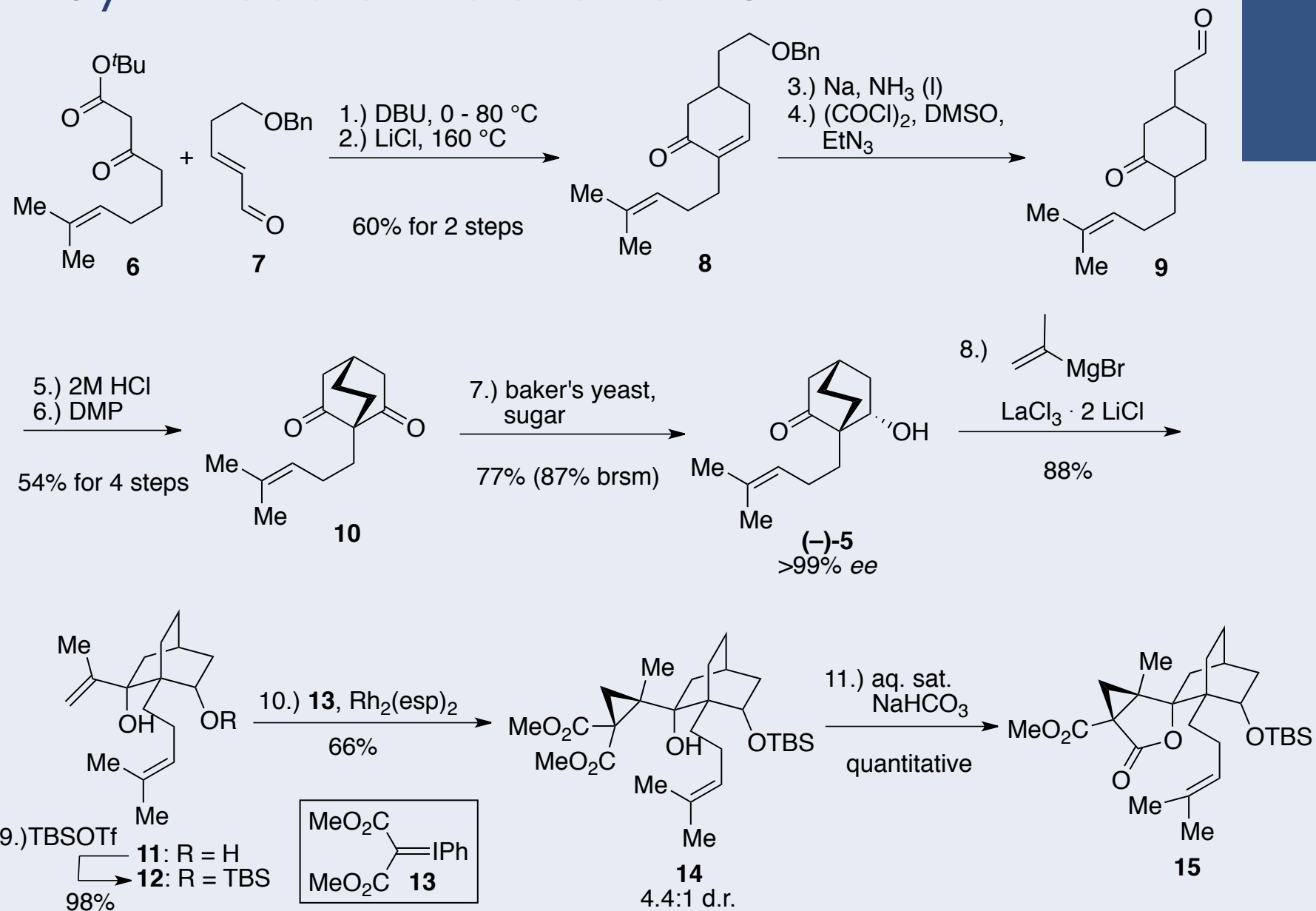


Retrosynthetic Analysis



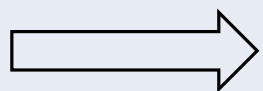
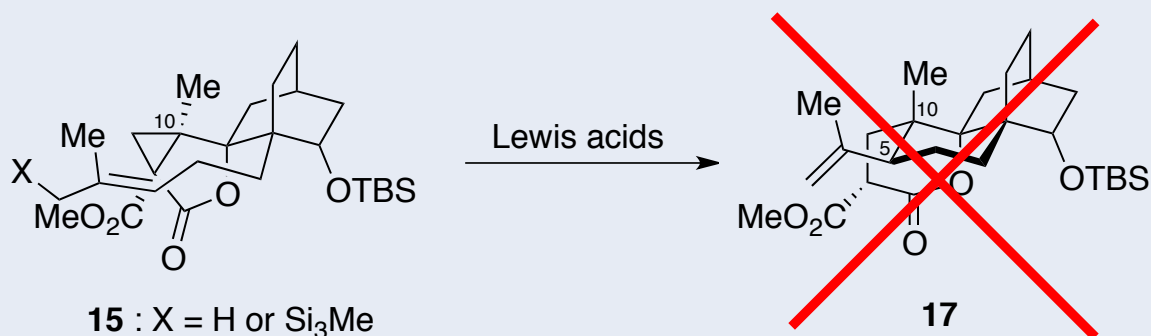
- Late-stage introduction of enone at C(16)
- Cyclopropane opening and cyclization cascade (*annulative cascade*)
- Construction of lactone and cyclopropane from hydroxyketone **5**
- Bicyclo[2.2.2]octane **5** could be obtained from β -ketoester **6** and enal **7**

Synthesis of Lactone 15



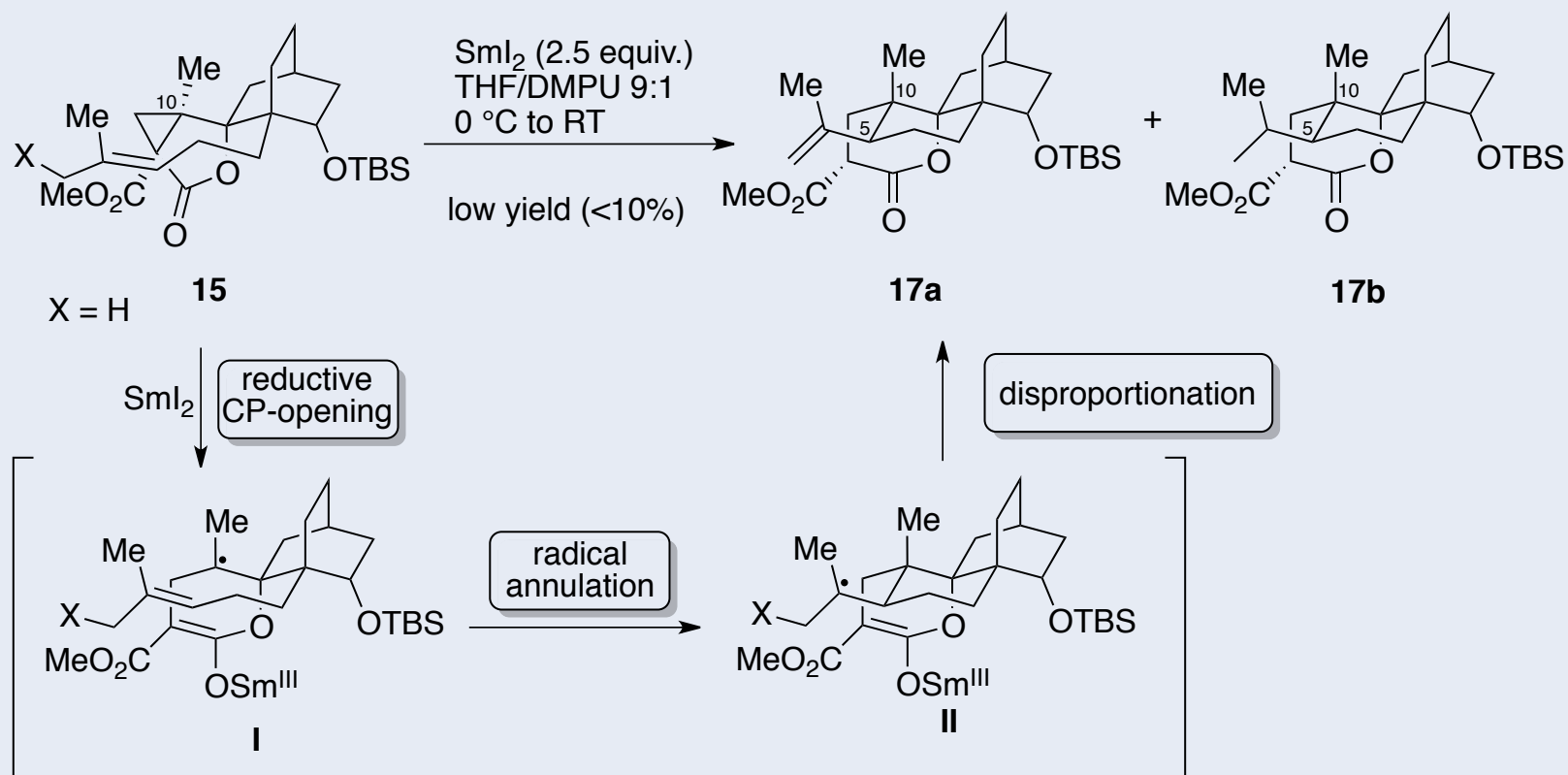
Annulative Cascade

Trisubstituted olefin would serve as nucleophile (e.g. $X = \text{H}, \text{SiMe}_3$) in the opening of the electrophilic cyclopropane in **15** to deliver tetracyclic product **17**



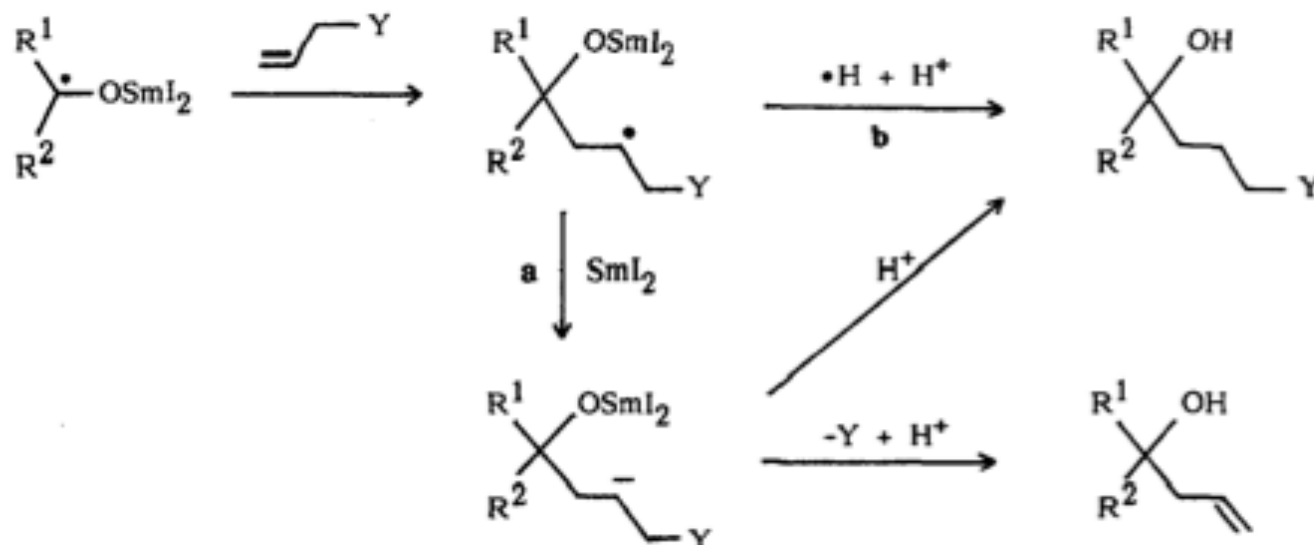
Reversal of reactivity, wherein the alkene would serve as an acceptor to a reactive, nucleophilic species at C(10) derived from reductive opening of the cyclopropane

Annulative Cascade

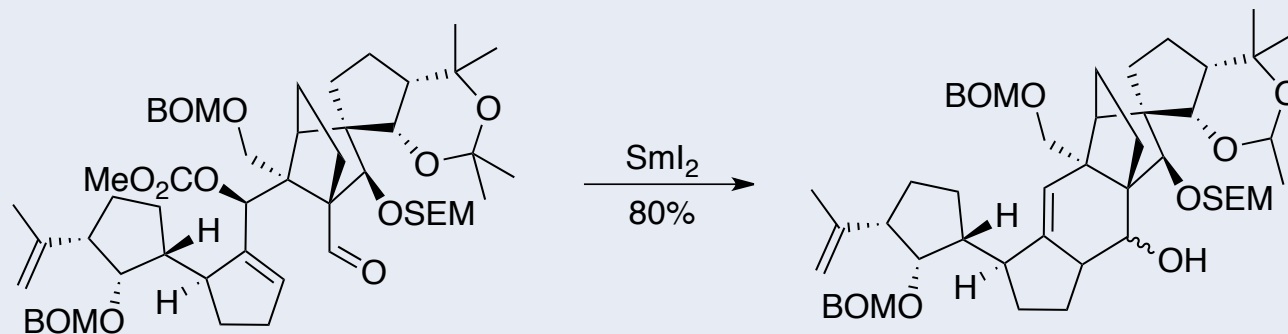


Speculation: offering the radical at C(4) a suitable leaving group (X) would enable a favorable termination pathway, leading to increased product formation?!?

Sml₂-Promoted Anion Radical Alkylation



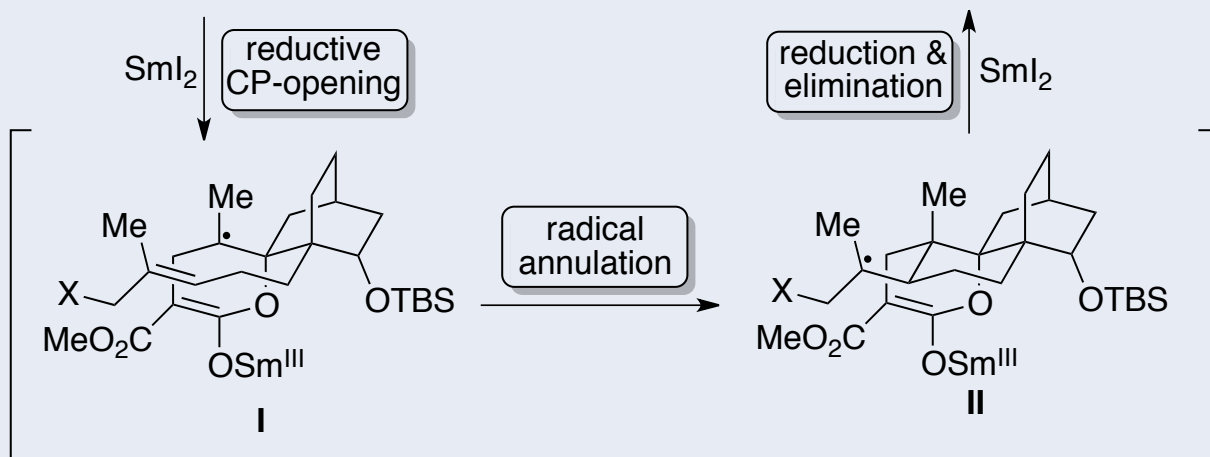
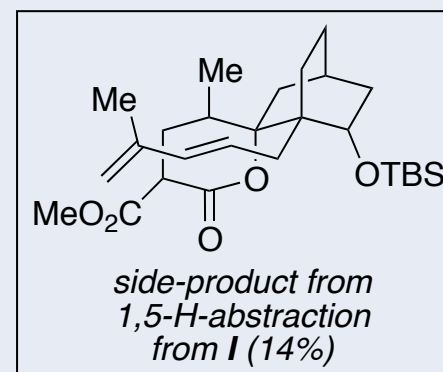
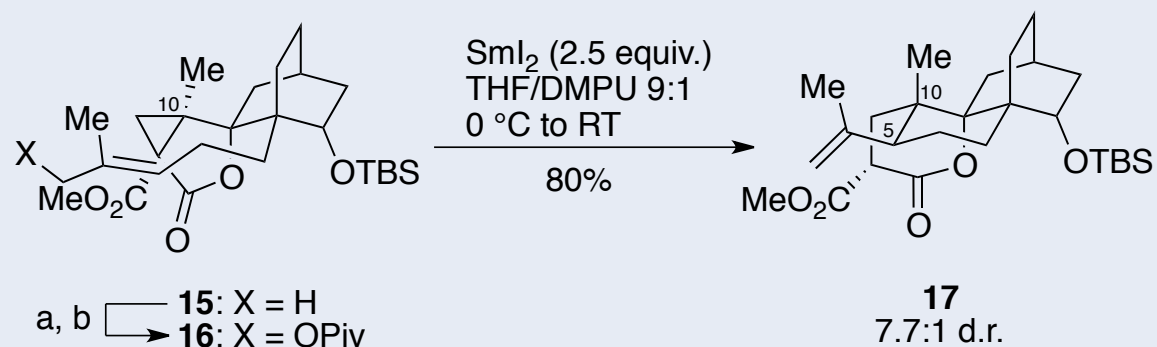
J. Inanaga *et al.* *Tet. Lett.* **1989**, 30, 2837.



Total Synthesis of
Vannusal B

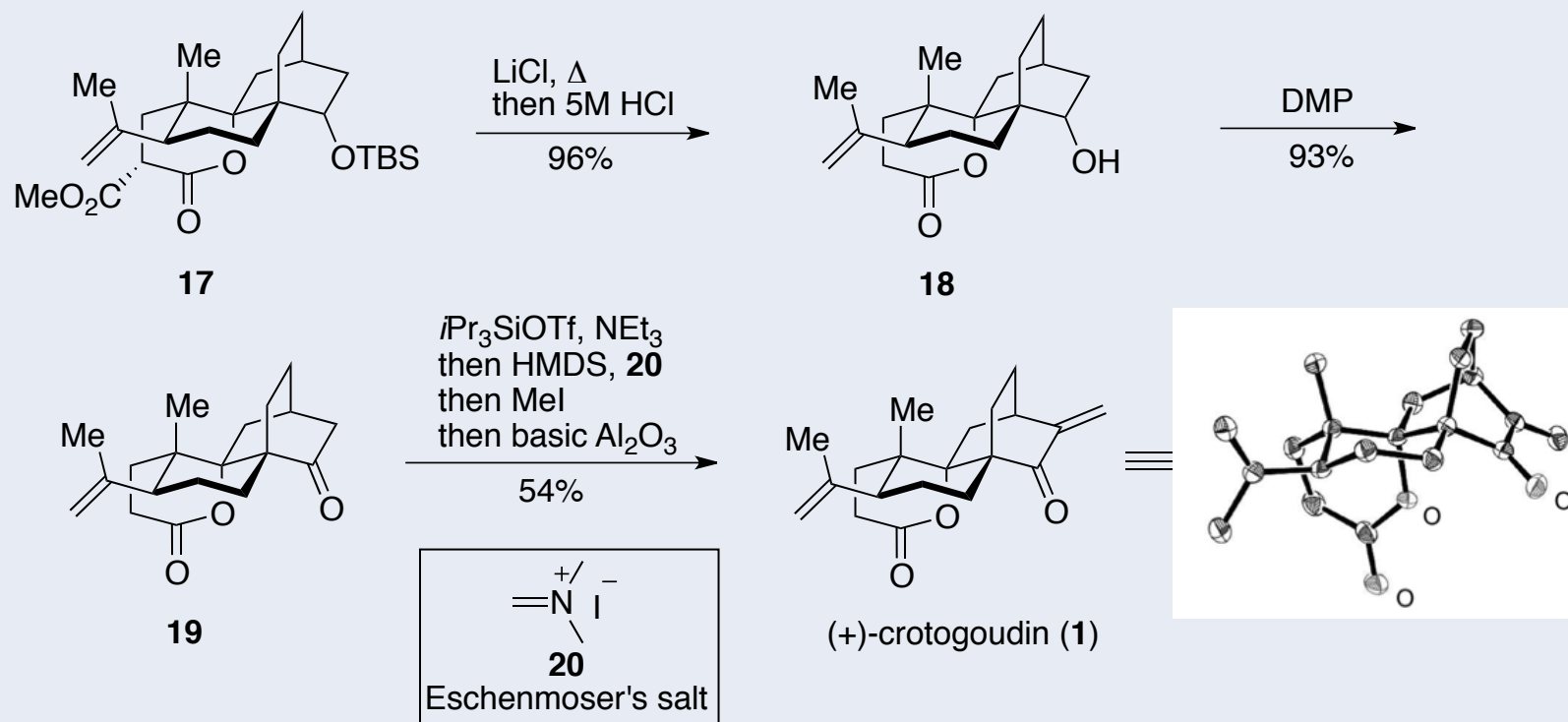
K. C. Nicolaou *et al.* *Angew. Chem. Int. Ed.* **2008**, 47, 8605.

Annulative Cascade



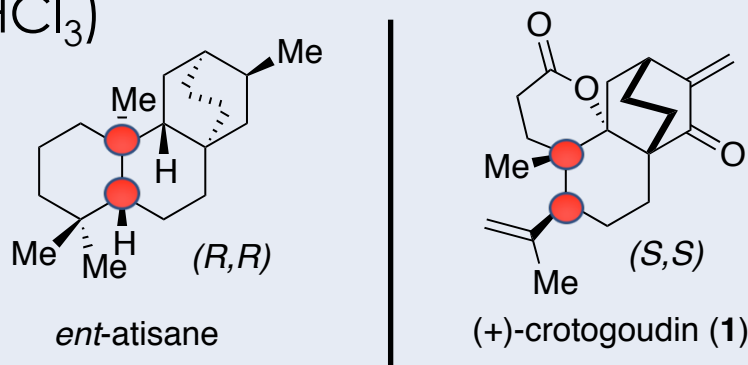
a.) SeO_2 , $t\text{BuO}_2\text{H}$ then NaBH_4 , 74%
 b.) Me_3COCl , 95%

Completion of the Synthesis



Conclusion

- All spectroscopic and physical data were in full agreement with already reported ones, except the optical rotation
- Synthetic: $[\alpha]_D^{20} = +29.6$ ($c = 0.4$, CHCl_3); Reported: $[\alpha]_D^{20} = +7$ ($c = 0.4$, CHCl_3)

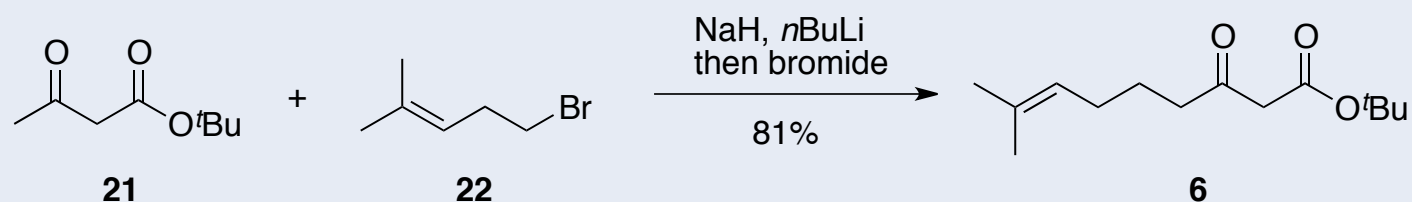


→ re-measurement of the optical rotation (→ $[\alpha]_D^{20} = -25.2$ ($c = 0.4$, CHCl_3) for **1**)

- Natural product is $(-)$ -crotogoudin with (R,R) -configuration

Preparation of Starting Materials 6+7

- Weiler dianion alkylation (*JACS* **1970**, 92, 6702.)



- A. Córdoba *et al.* *Eur. J. Org. Chem.* **2012**, 398.

