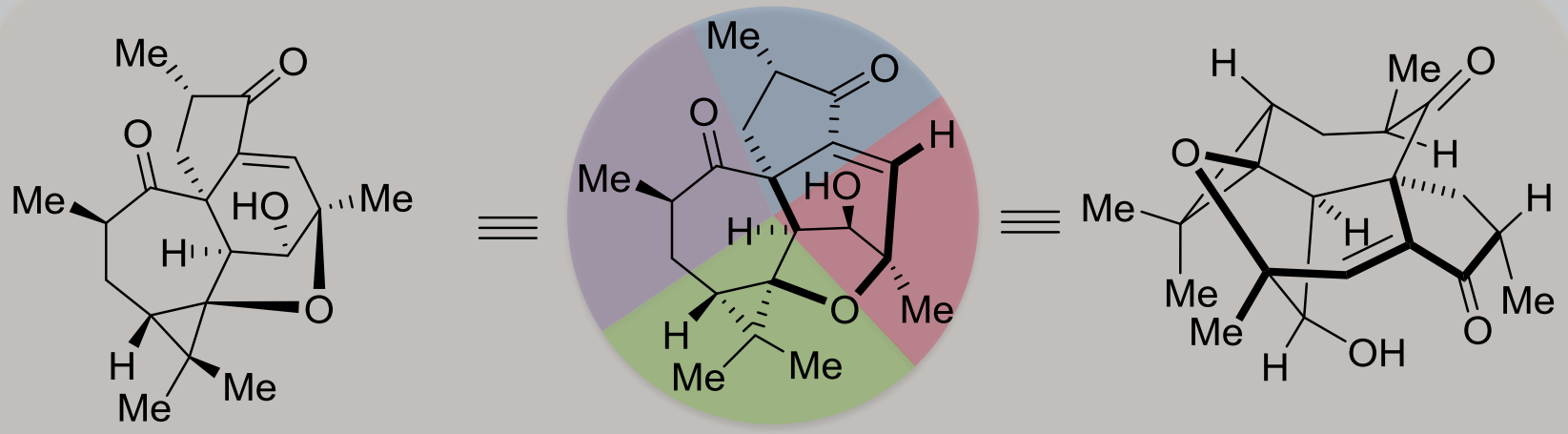
Total Synthesis of (+)-Steenkrotin A

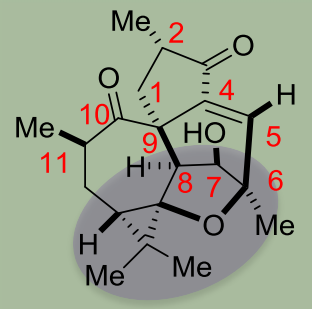
The PhD work in Hanfeng Ding group during 2012.06 - 2015.08 at Zhejiang University



Steenkrotin A

Saiyong Pan, 16/12/2015
Guangbin Dong Group at UT austin

Content



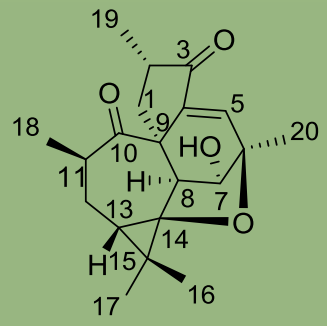
- The background of steenkrotin A

- The initial strategy toward [5,6,7] tricycle of steenkrotin A
- Diels–Alder cycloadditon as key step to synthesize [5,6,7] tricycle of steenkrotin A
- The conquest of gem–dimethylcyclopropanol (the most challenging moiety)

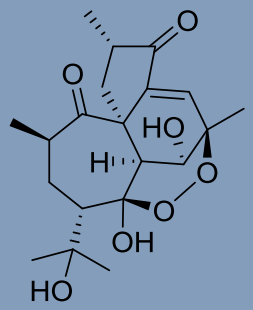
- The revised strategy toward C11 demethyl-steenkrotin A
- Total synthesis of (+)-steenkrotin A

Isolation of (+)-Steenkrotin A

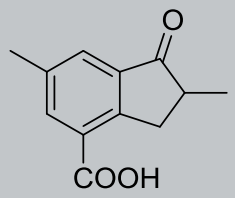




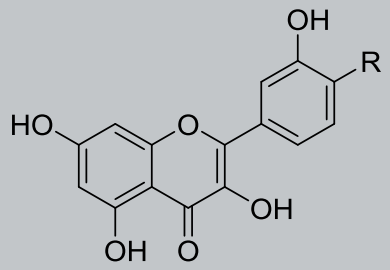
steenkrotin A (1)



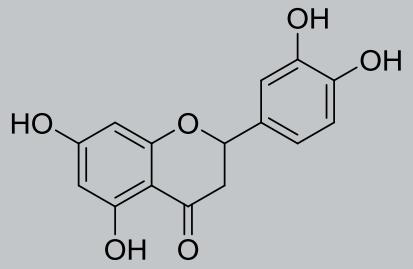
steenkrotin B (2)



indane derivative (3)



R=OH, quercetin (4)
R=I, taxmarixetin (5)

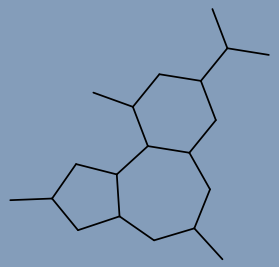


eriodictyol (6)

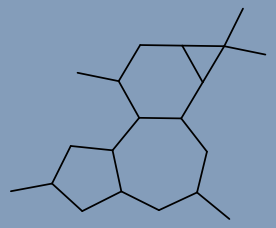
- The diterpenoid (+)-steenkrotin A was isolated by Hussein and co-workers from the leaves of ***Croton steenkampianus*** *(Euphorbiaceae)* in 2008, which displayed mild antiplasmodial activities of 15.8 (D10), 9.1 (W2).
- The intricate [3,5,5,6,7] pentacycliccarbon framework contains eight stereogenic centers, of which six are contiguous including one all-carbon quaternary center.

(1) Adelekan, A. M.; Prozesky, E. A.; Hussein, A. A.; Ureña, L. D.; van Rooyen, P. H.; Liles, D. C.; Meyer, J. J. M.; Rodríguez, B. *J. Nat. Prod.* **2008**, *71*, 1919.

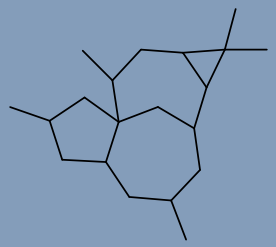
Representative natural products of Euphorbiaceae



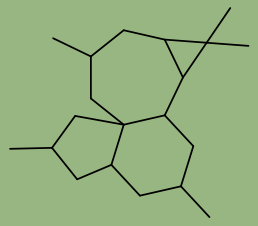
daphnane



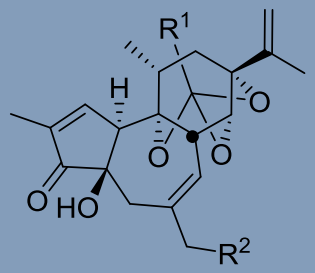
tigliane



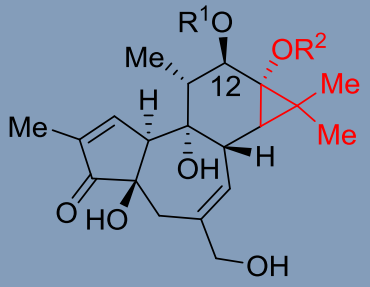
ingenane



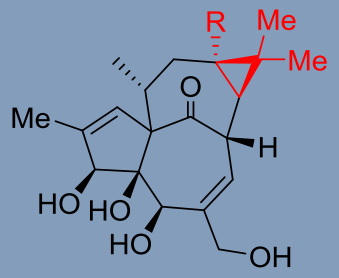
steenkrotane



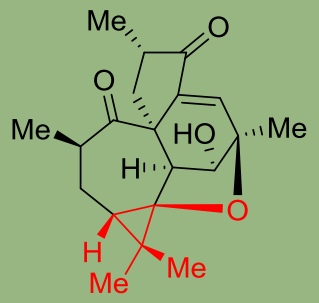
resinferonol



$R^1=R^2=H$, phorbol
$R^1=CO(CH_2)_{12}CH_3$
R^2=Ac, PMA



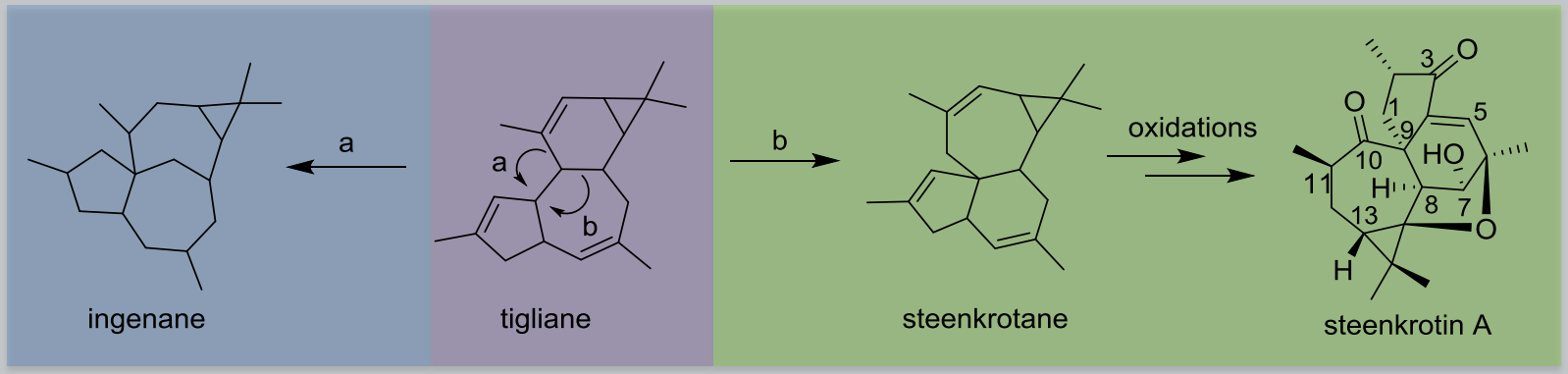
R=H, ingenol
R=OH, 13-oxyingenol



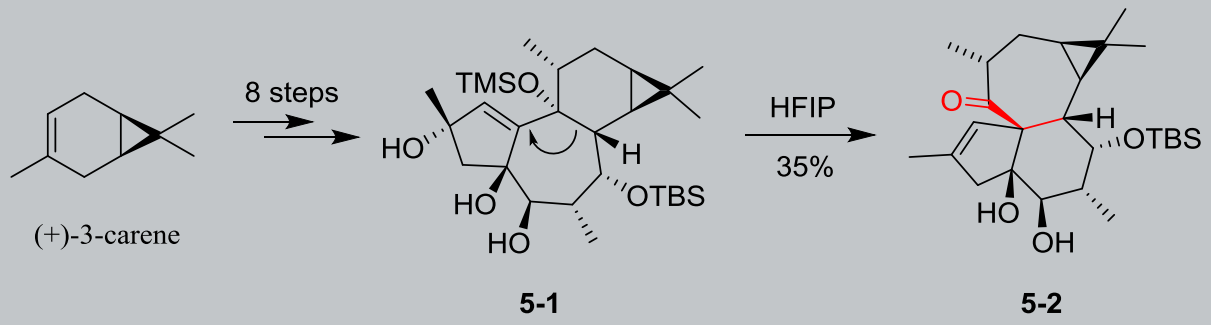
steenkrotin A (1)

(1) Evans, F. J. *Boca Raton: C. R. C. Press* **1986**.
(2) Kidd, J. G.; Rous, P. J. *J. Exp. Med.* **1938**, *68*, 173.

Biosynthesis of Steenkrotin A

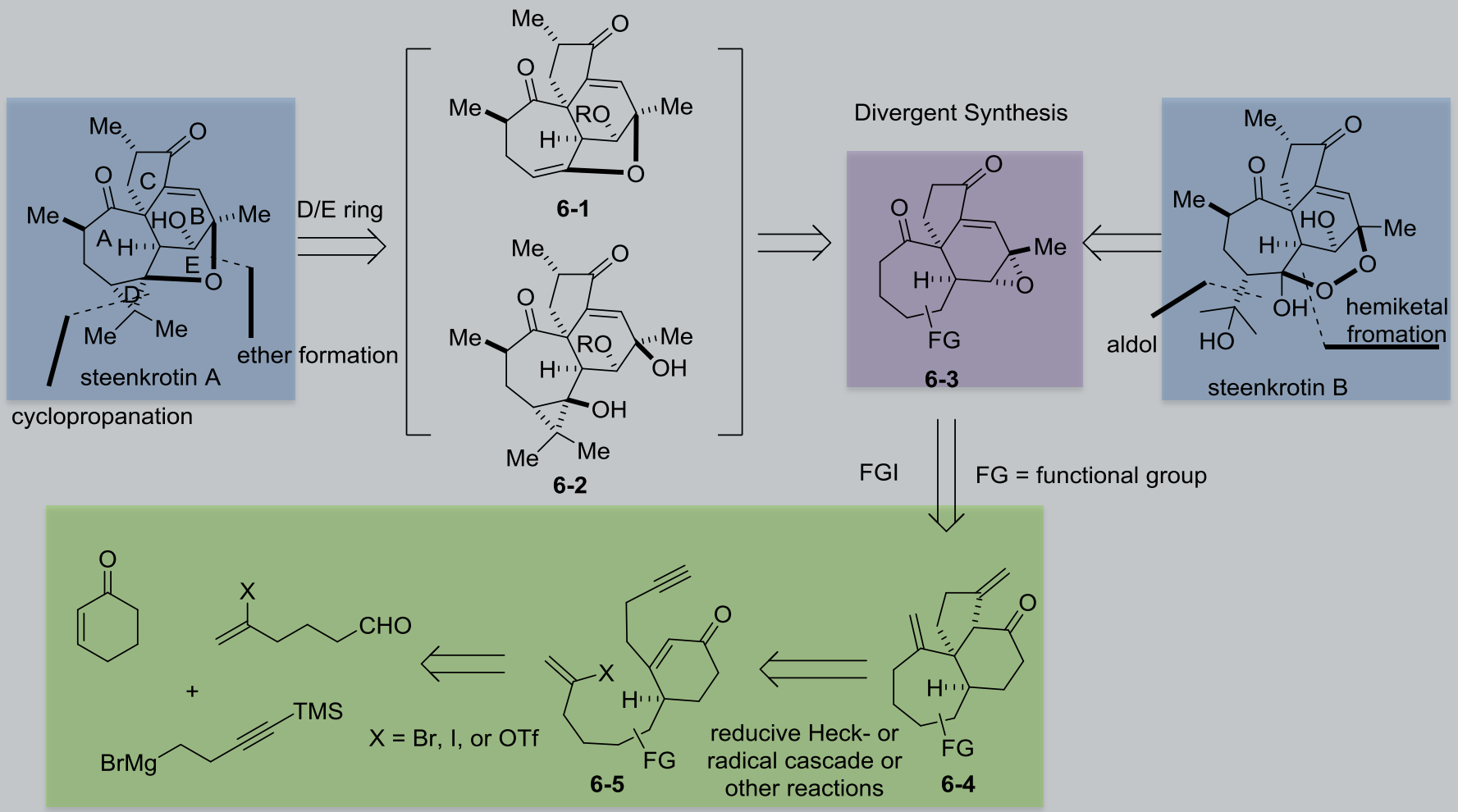


Baran's work on (+)-ingenol

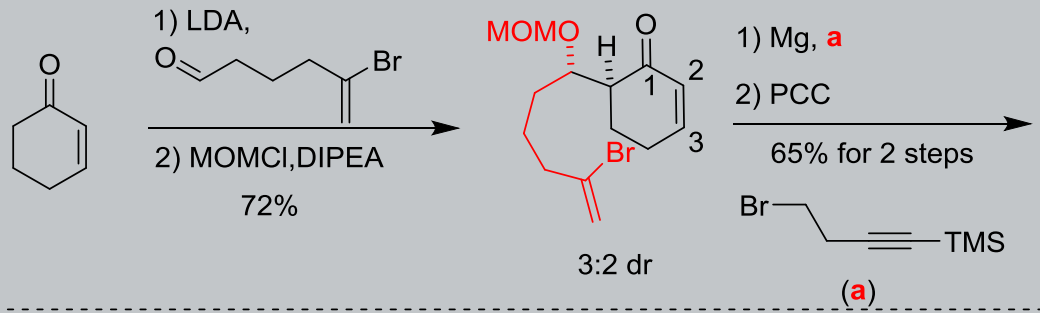


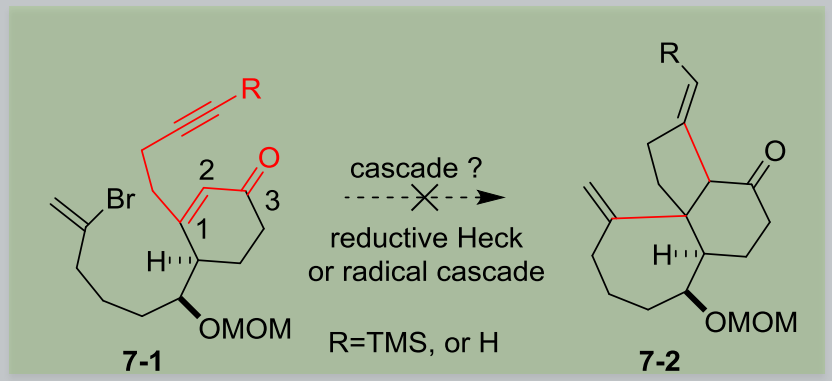
(1) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423.
(2) Adolf, W. H., E. *Isr. J. Chem.* **1977**, *16*, 75.

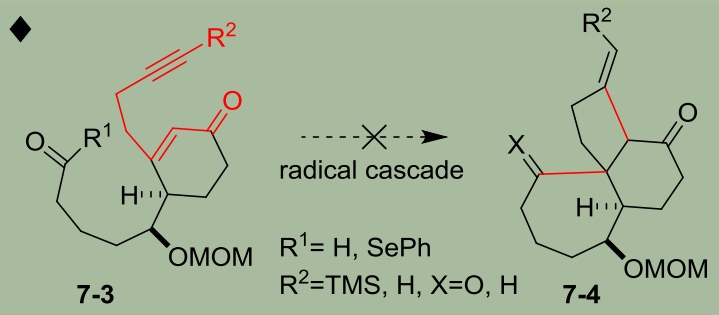
The initial Strategy toward steenkrotin A

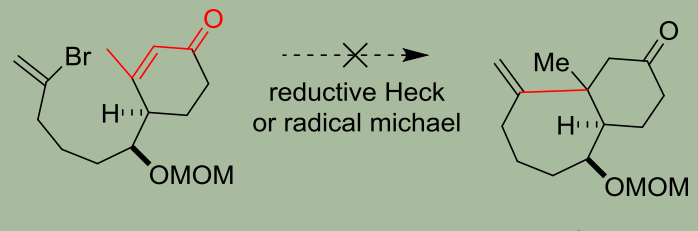


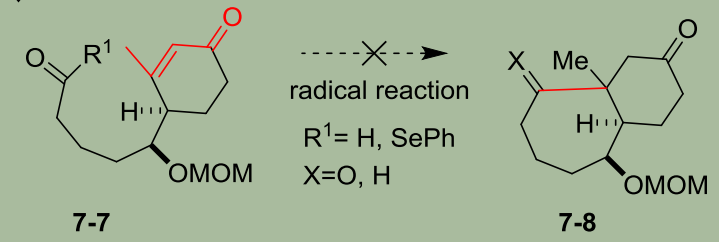
Representative synthesis of cascade substrates

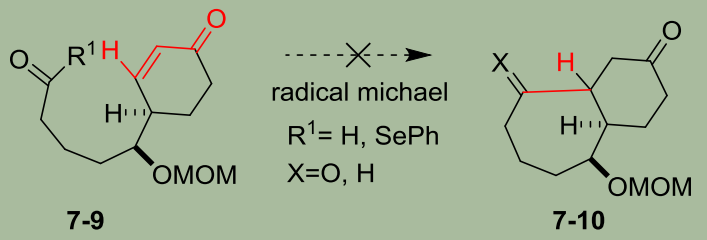




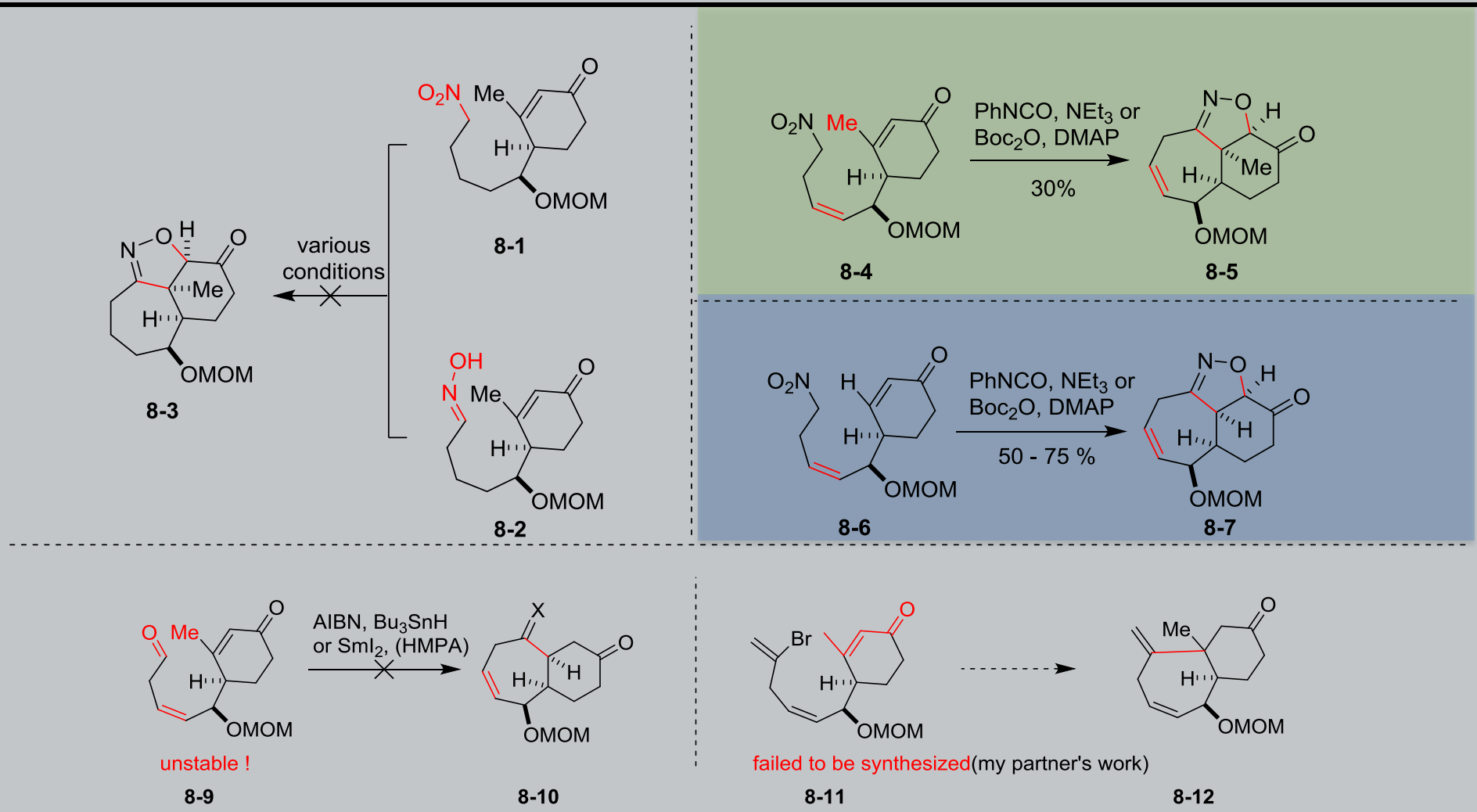




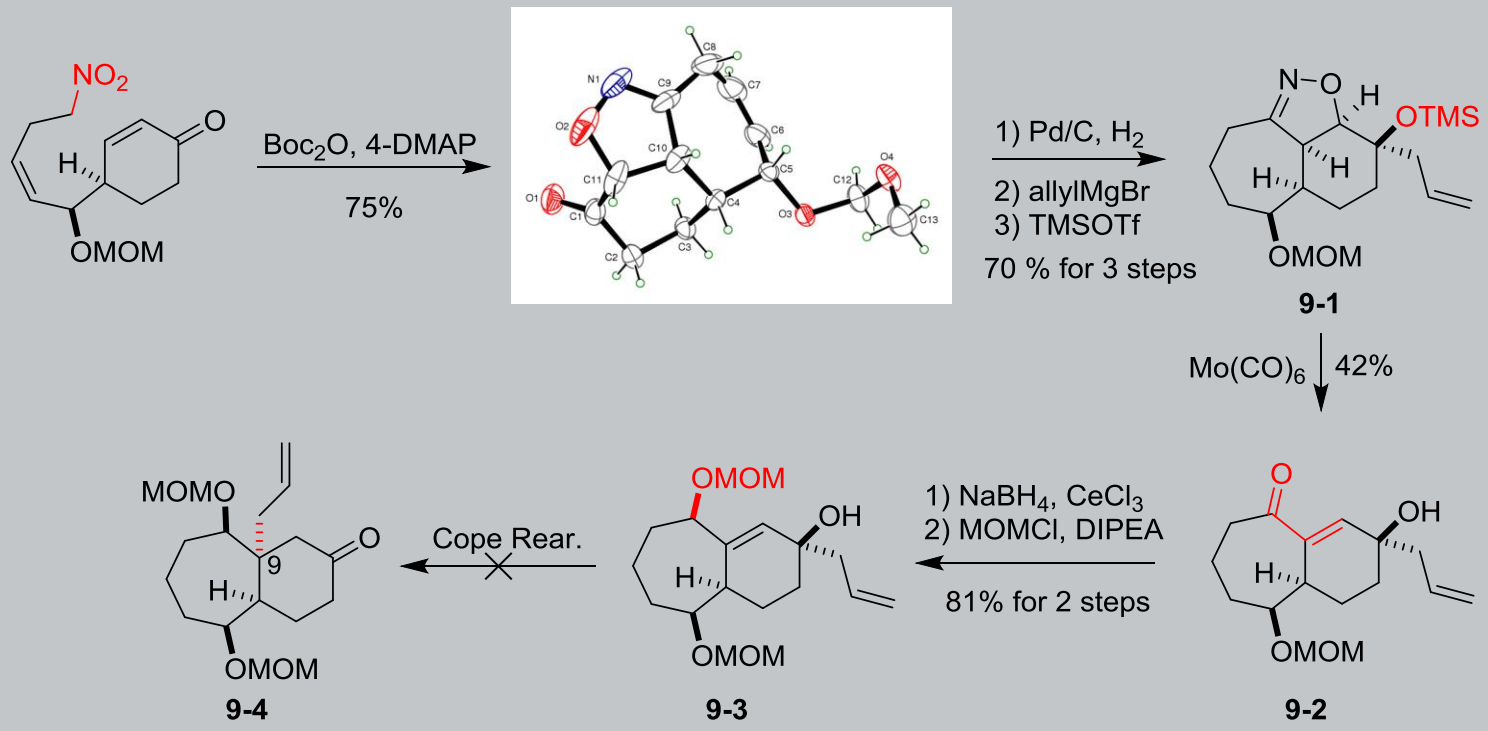




Intramolecular nitrile oxide/alkene [3+2] cycloaddition

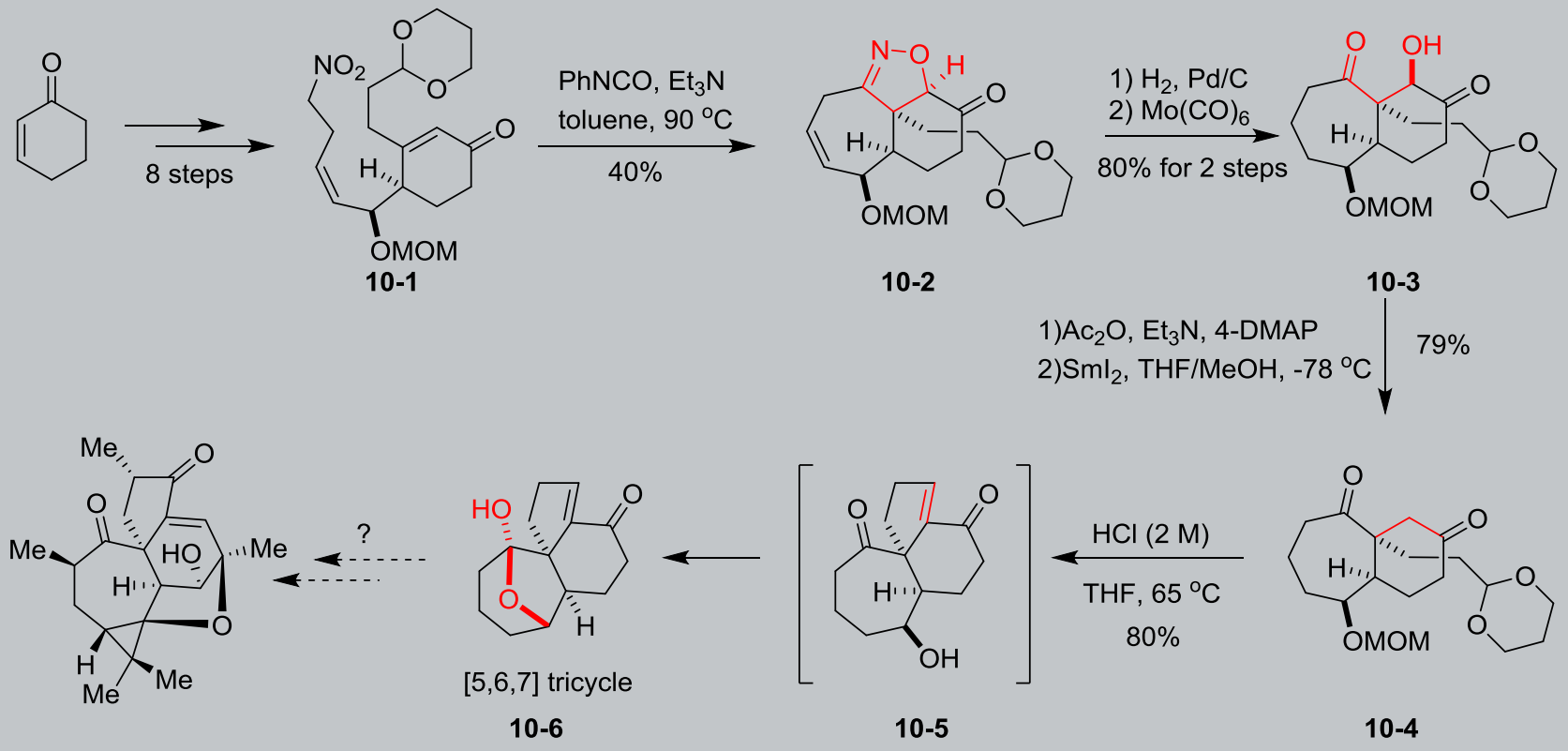


Synthesis of Cope rearrangement substrate



Due to failling to construct the quaternary center and the long sequence of this strategy, I decide to give up this strategy. At the later time, my partner using the similar [3+2] stragtegy synthesized the [5,6,7] structure of steenkrotin A, although in low yield!

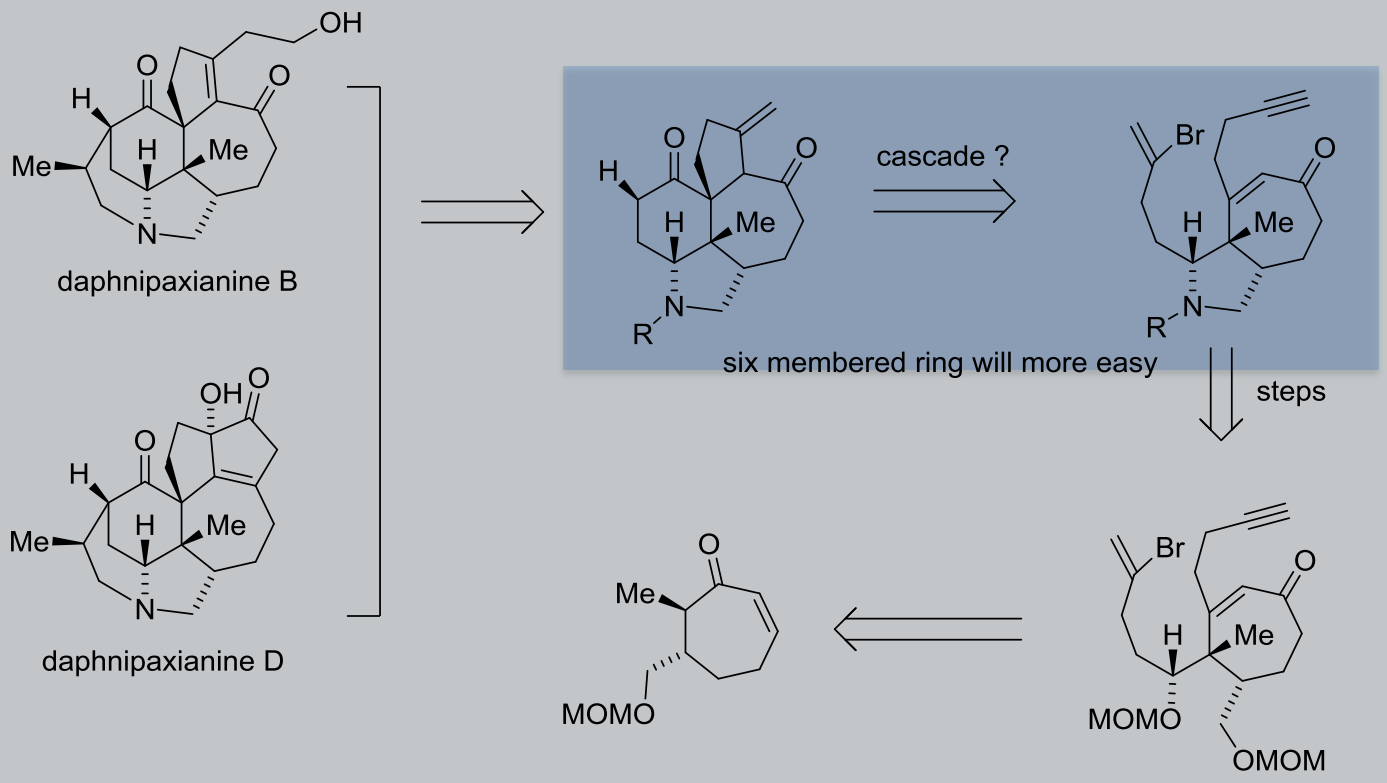
Jun Xuan's Synthesis of [5,6,7] structure of steenkrotin A



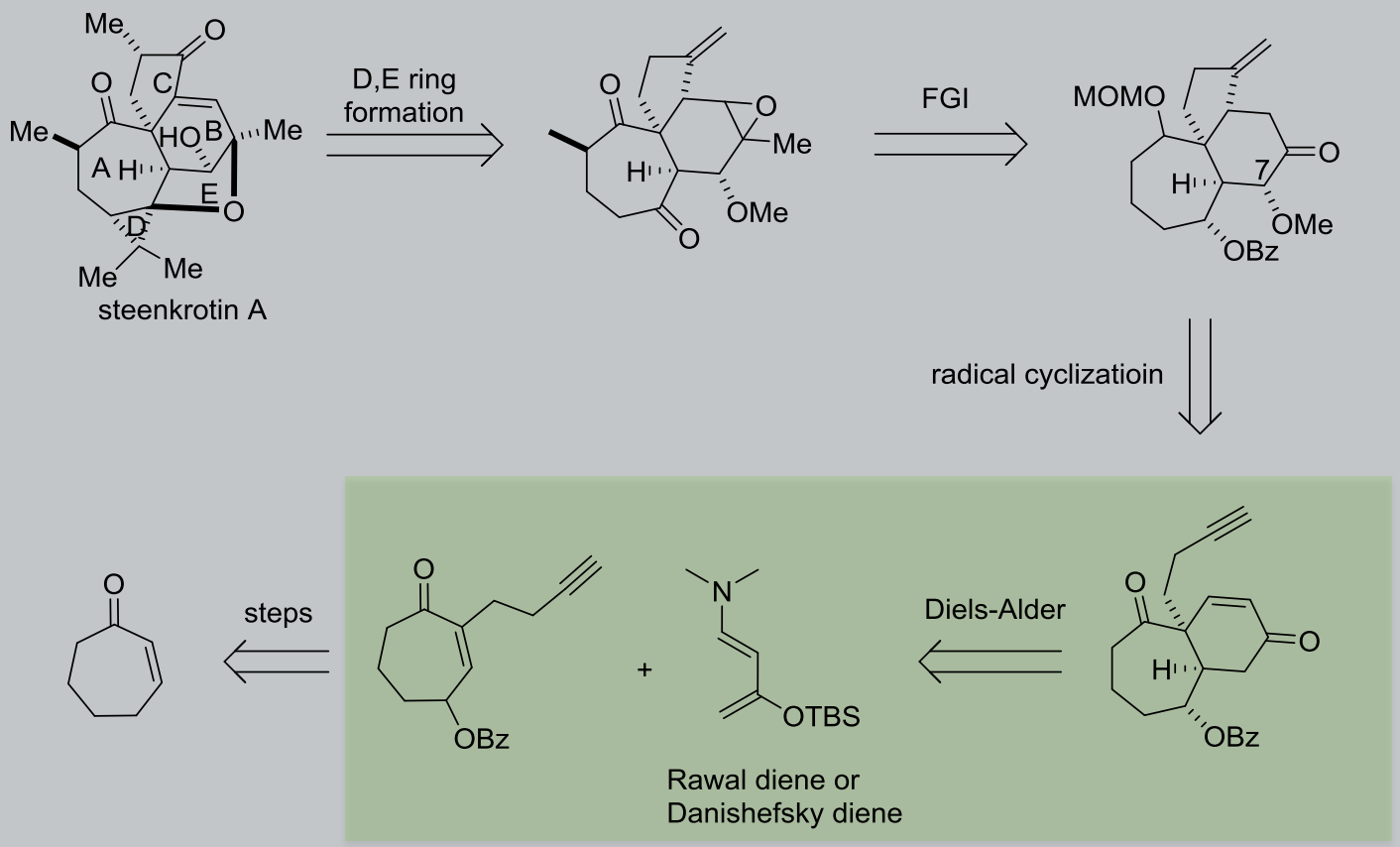
At this stage we get the tricycle structure of steenkrotin A, it seems we will furnish it in the near furture. However, it just the beginning of this game!

(1) Jun Xuan, † Saiyong Pan, † Yuanbao Zhang, Bin Ye, Hanfeng Ding.* *Org. Biomol. Chem.* **2015**, *13*, 1643-1646.
(†J.X. and S.P. contributed equally)

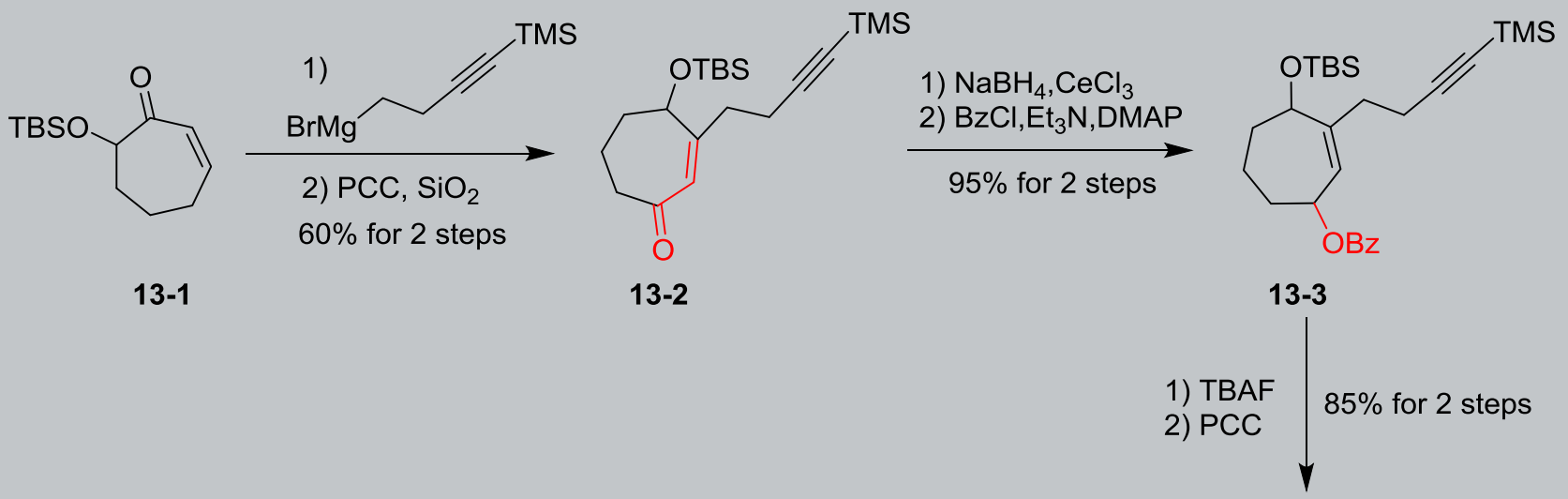
The failed strategy was used to daphnipaxianine D

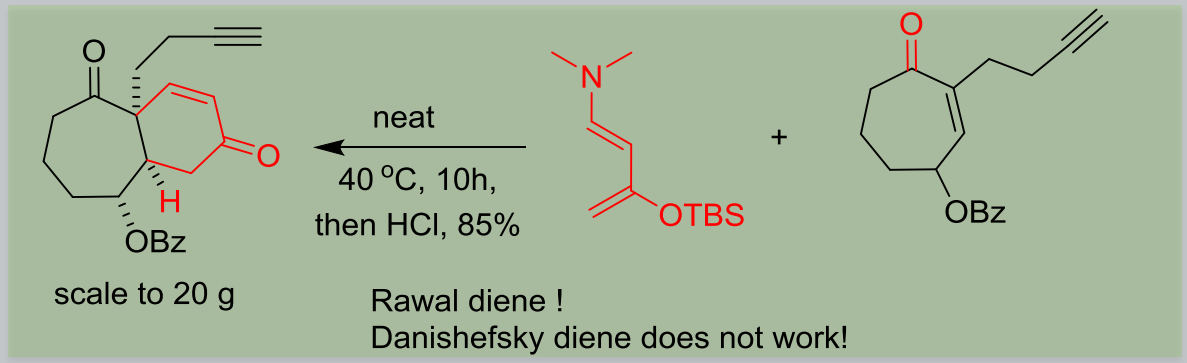


The new strategy based on Diels-Alder Cycloaddition

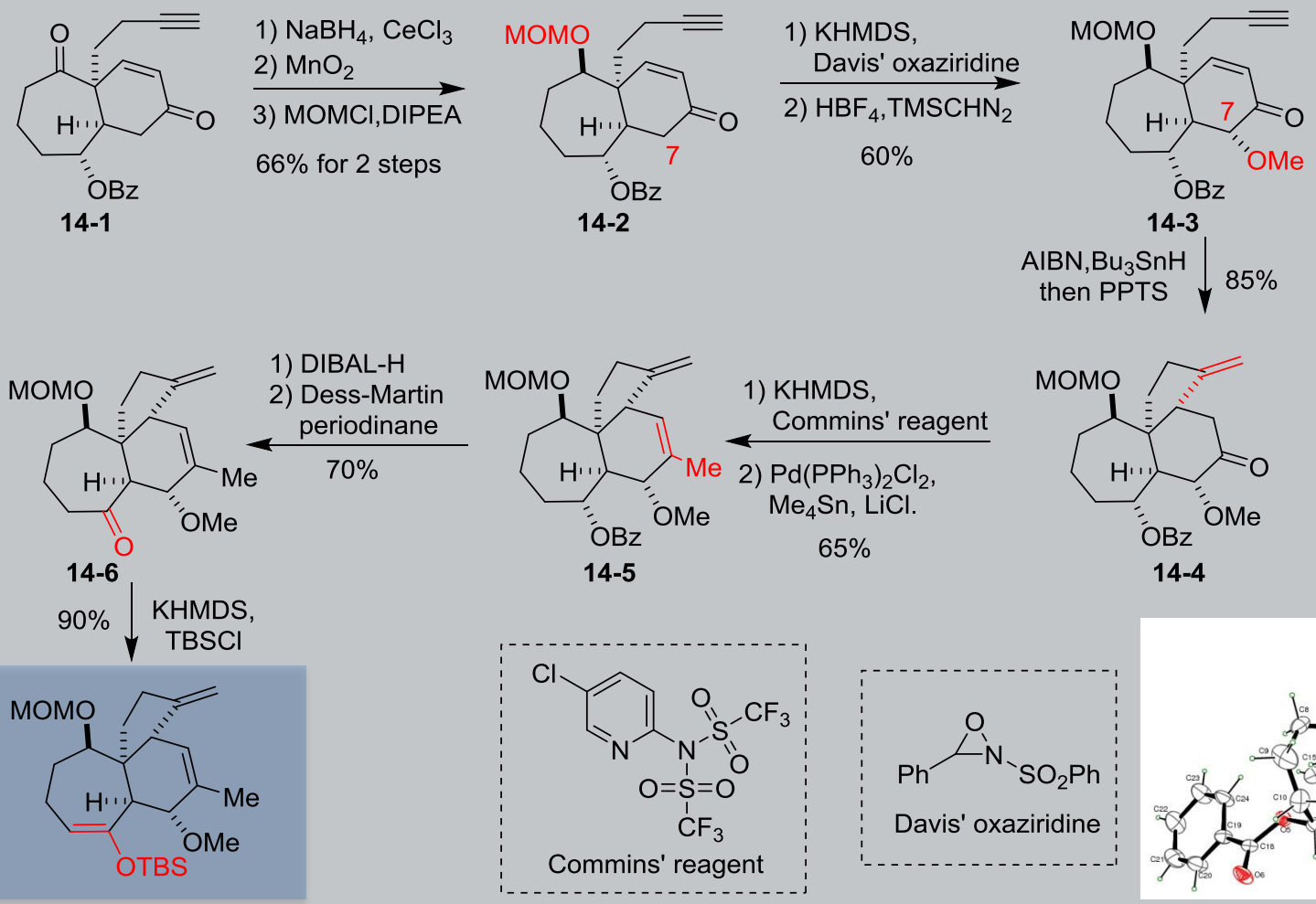


Intermolecular Diels-Alder cycloaddition

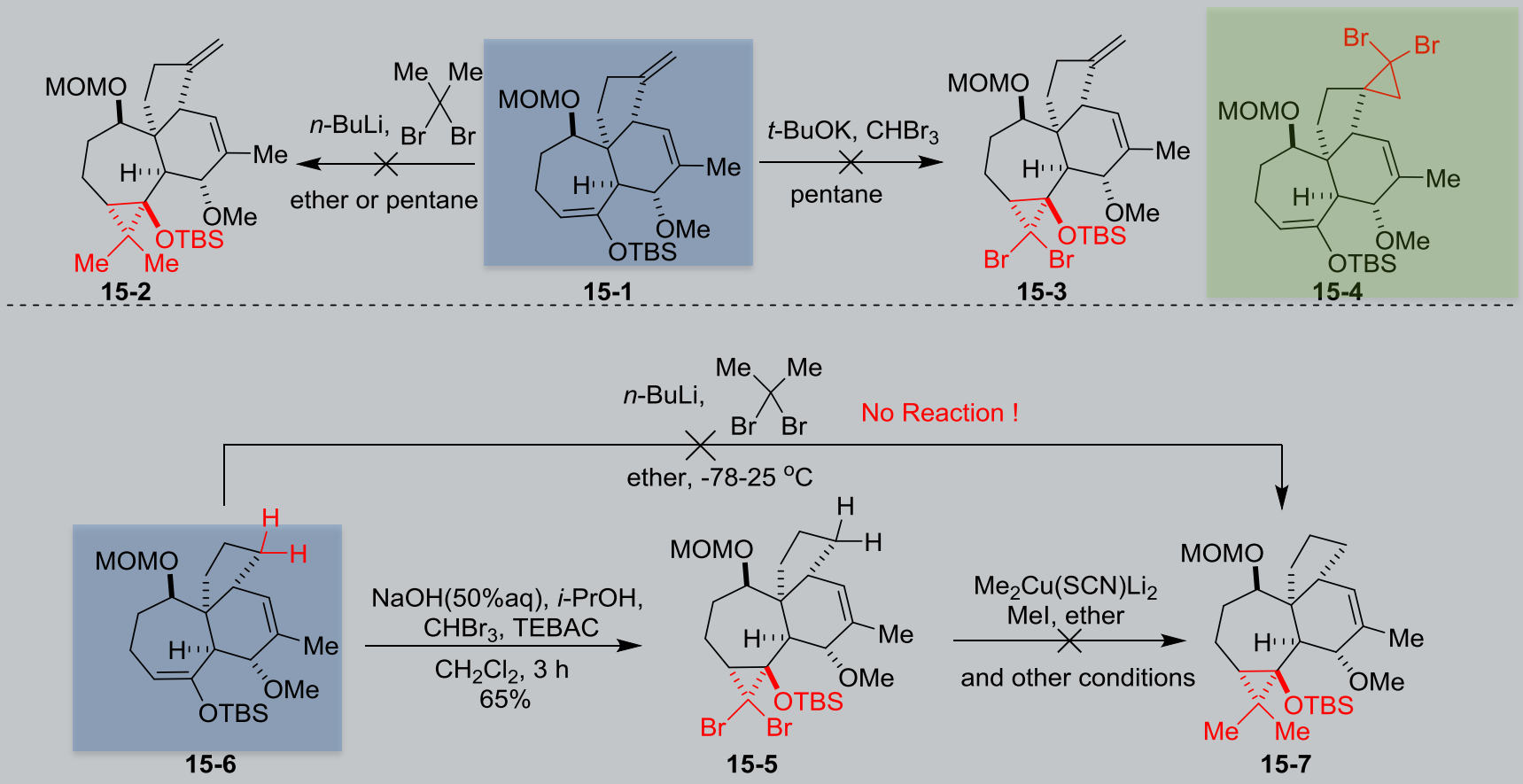




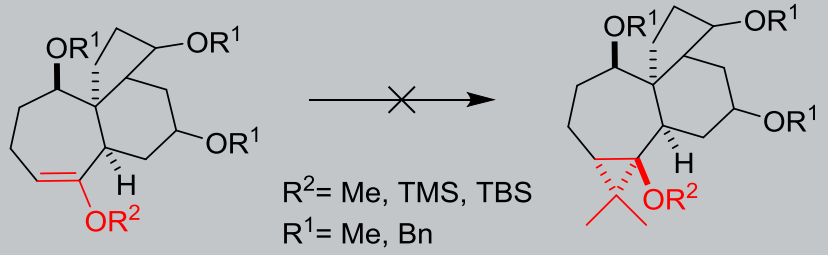
Synthesis of [5,6,7] substrate for cyclpropanation



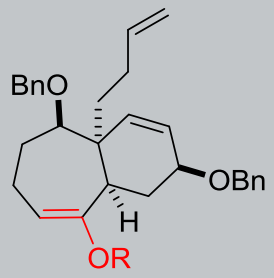
Attempt to synthesis of gem–dimethylcyclopropanol



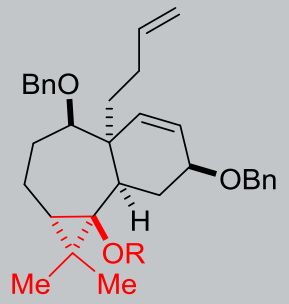
More substrate toward gem–dimethylcyclopropanol



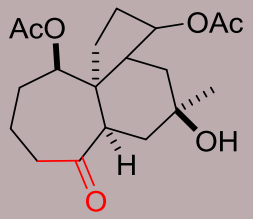
R^2= Me, TMS, TBS
R^1= Me, Bn



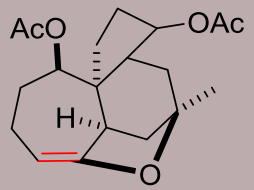
R= Me, TMS, TBS



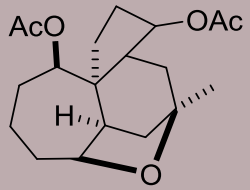
My partner's work



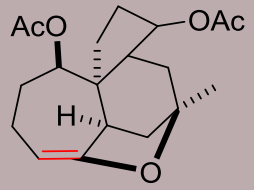
16-1



16-2



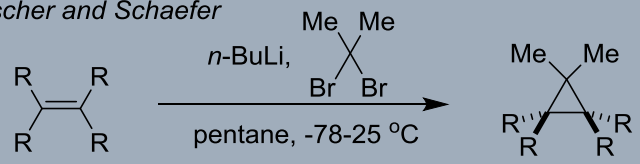
16-3



16-4

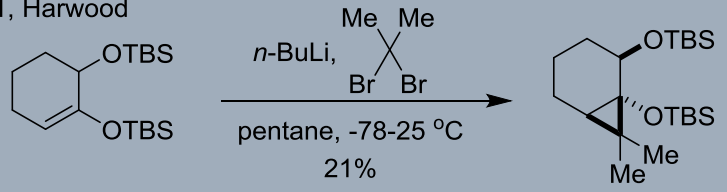
Review of gem–dimethylcyclopropanol

1981, Fischer and Schaefer

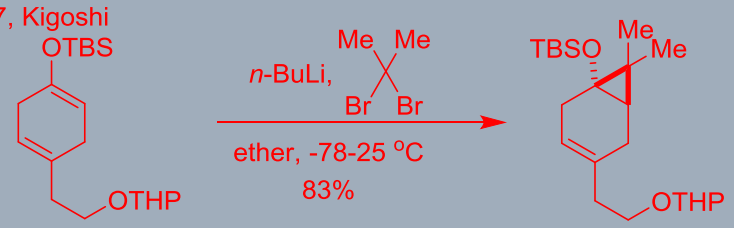


Olefin	Olefin recovered (%)	Yield relative to olefin consumed (%)
$(CH_3)_2C=C(CH_3)_2$	45	46
Cyclooctatetraene	24	16
Cyclohexene	55	27
2-Norbornene	68	-
Ph-CH=CH_2	12	44
Ph-CH=CH-OCH_3	78	6

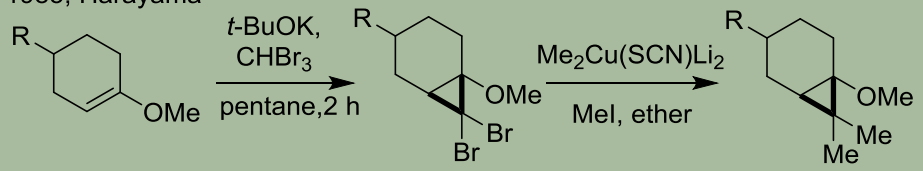
2001, Harwood



2007, Kigoshi



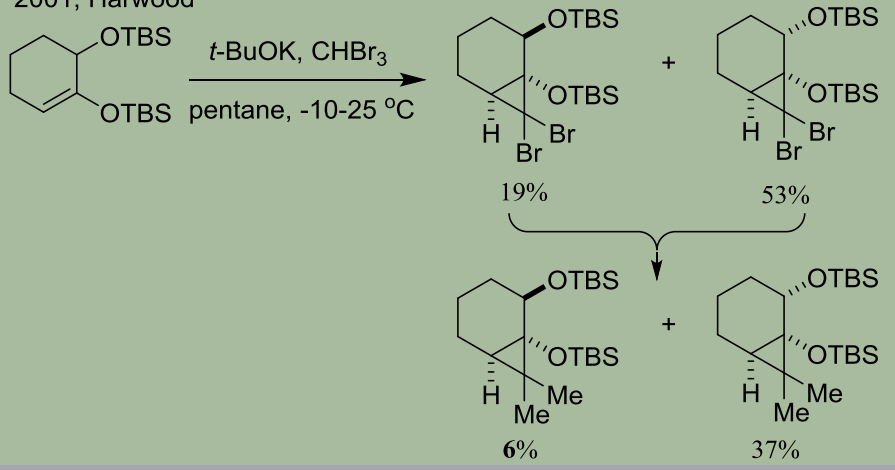
1985, Harayama



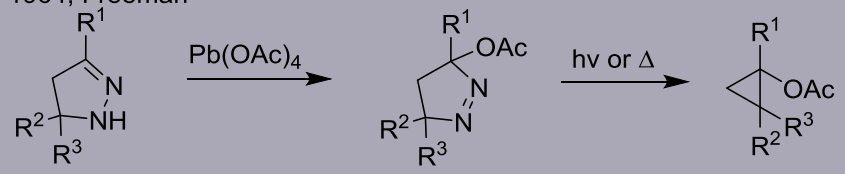
R= H 91%
R=t-Bu 80%

R= H 44%
R=t-Bu 71%

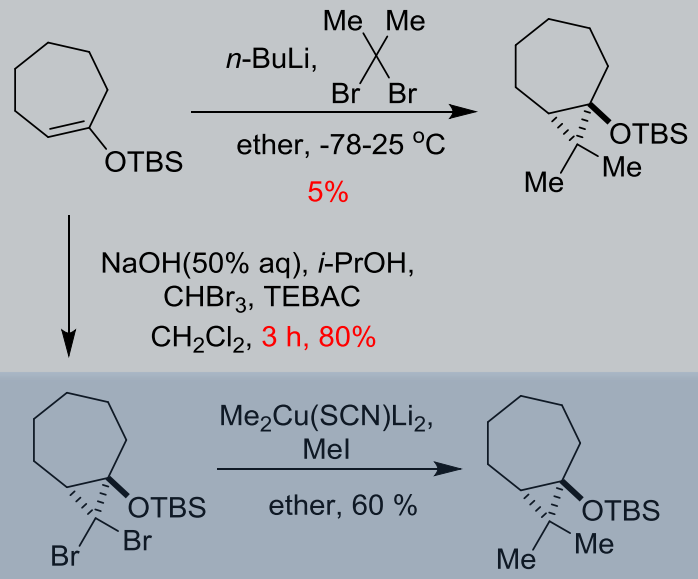
2001, Harwood

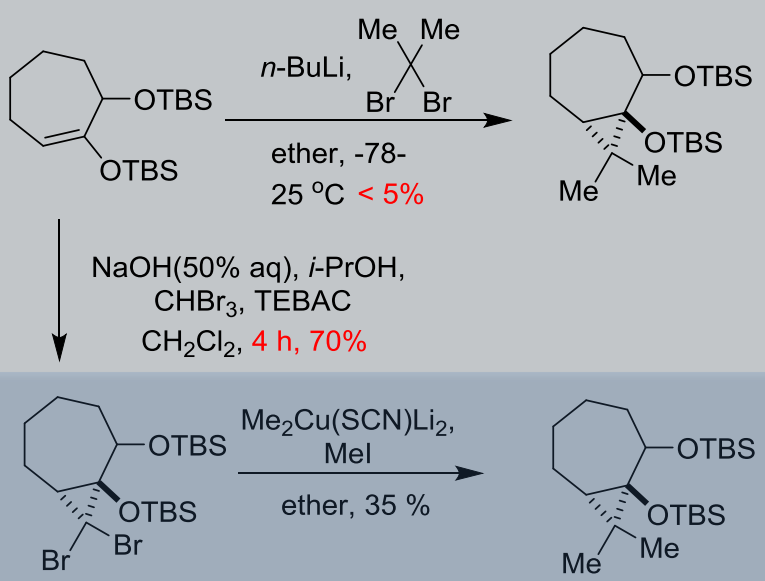


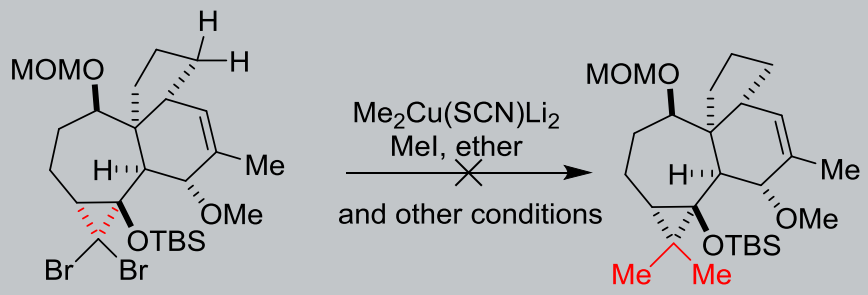
1964, Freeman



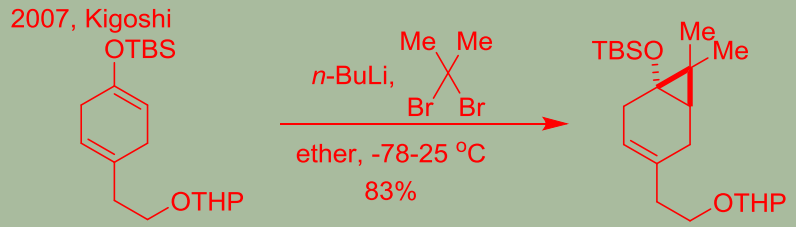
Model studies toward gem–dimethylcyclopropanol





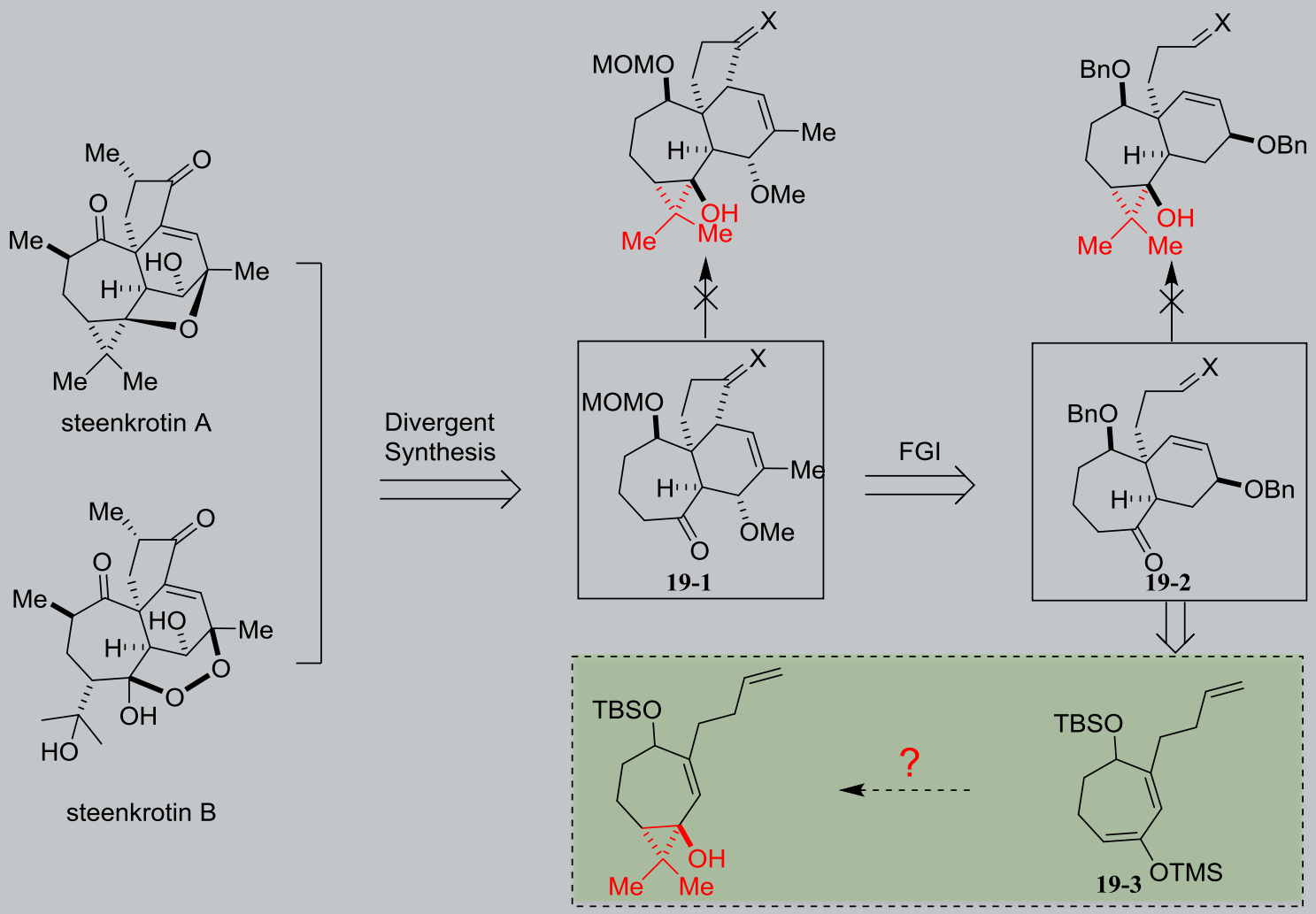


may be too crowded !



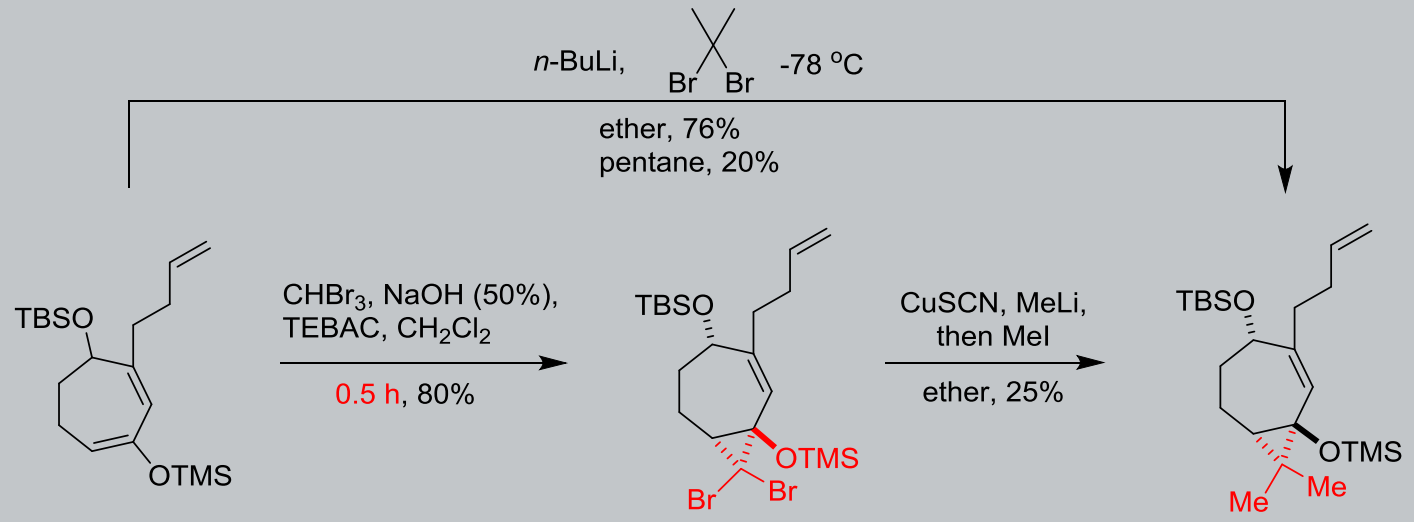
why this substrate is so active ?

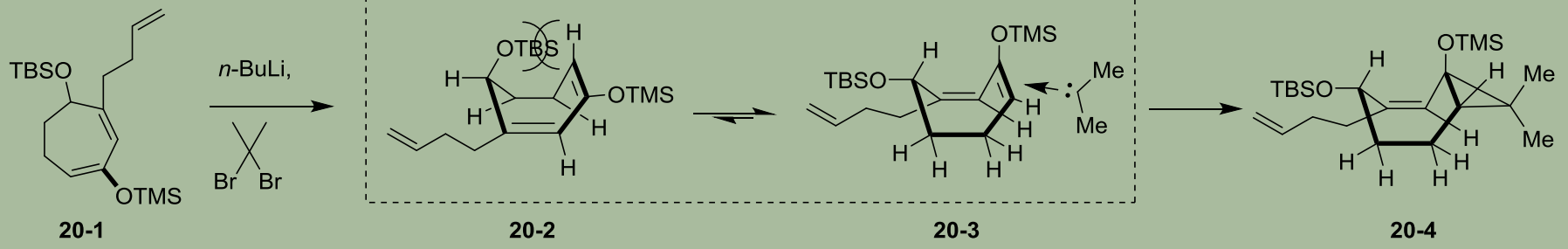
Analysis of gem–dimethylcyclopropanol



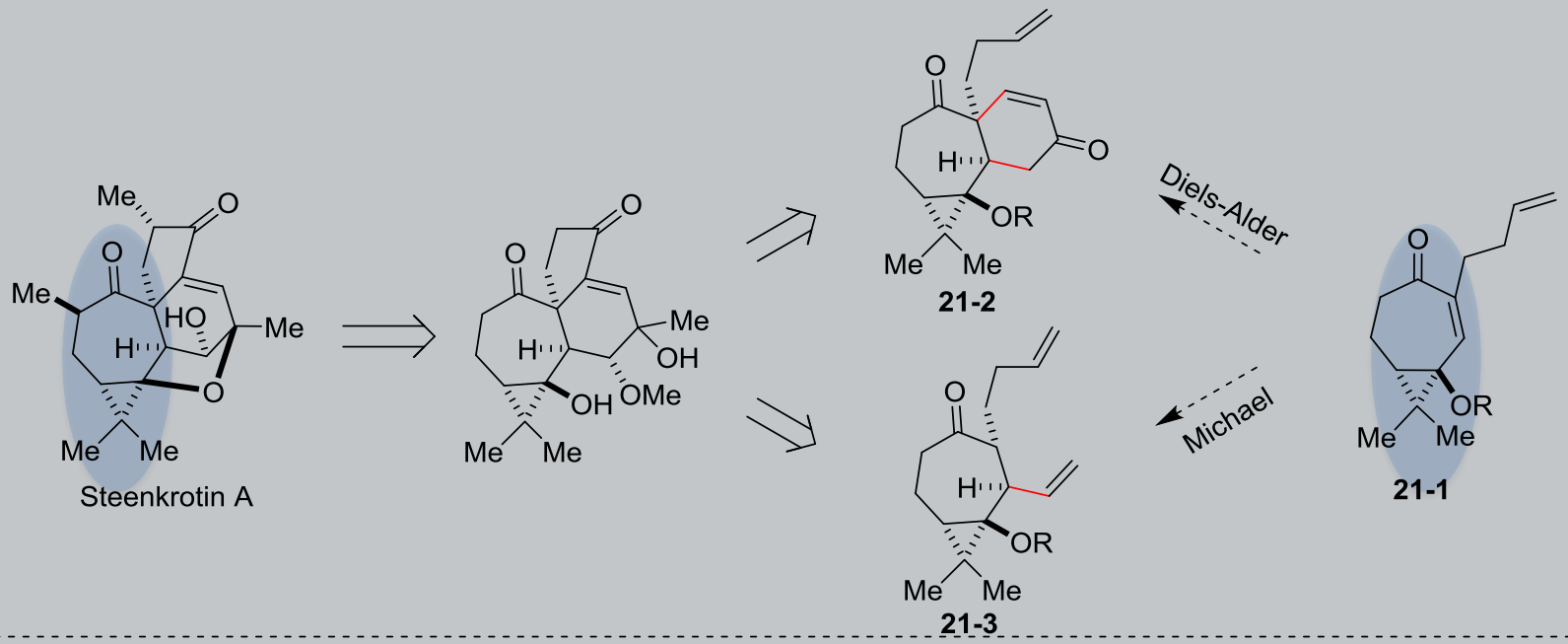
Due to the Diels-Alder strategy latter was used to synthesize steenkrotin B, so theses results is not published.

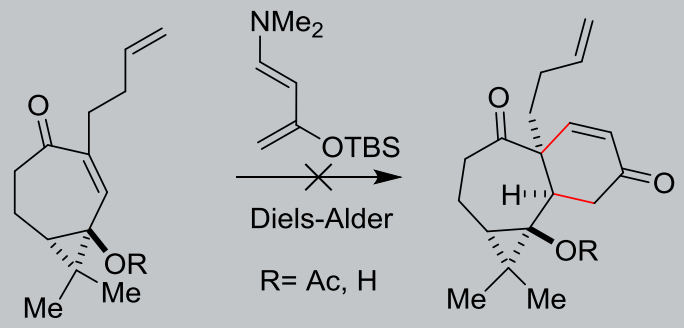
Conquest of gem–dimethylcyclopropanol

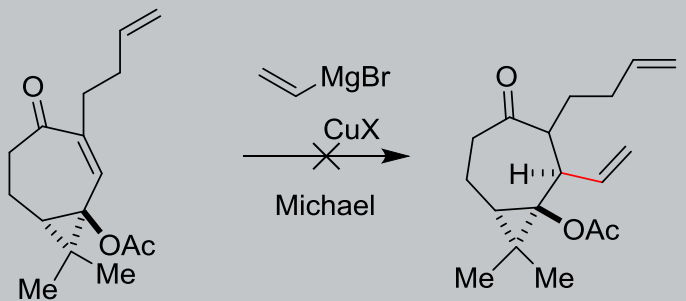




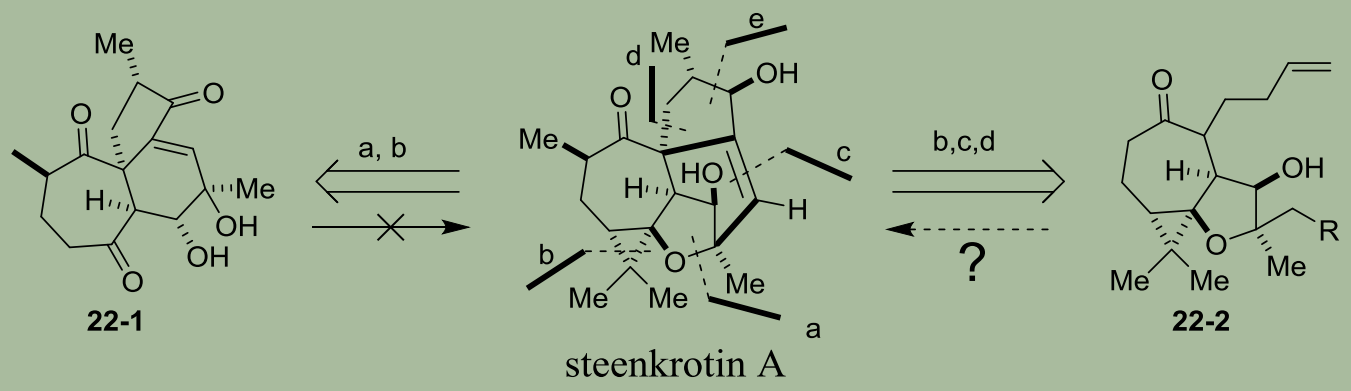
The initial idea based on [3,7] bicycle

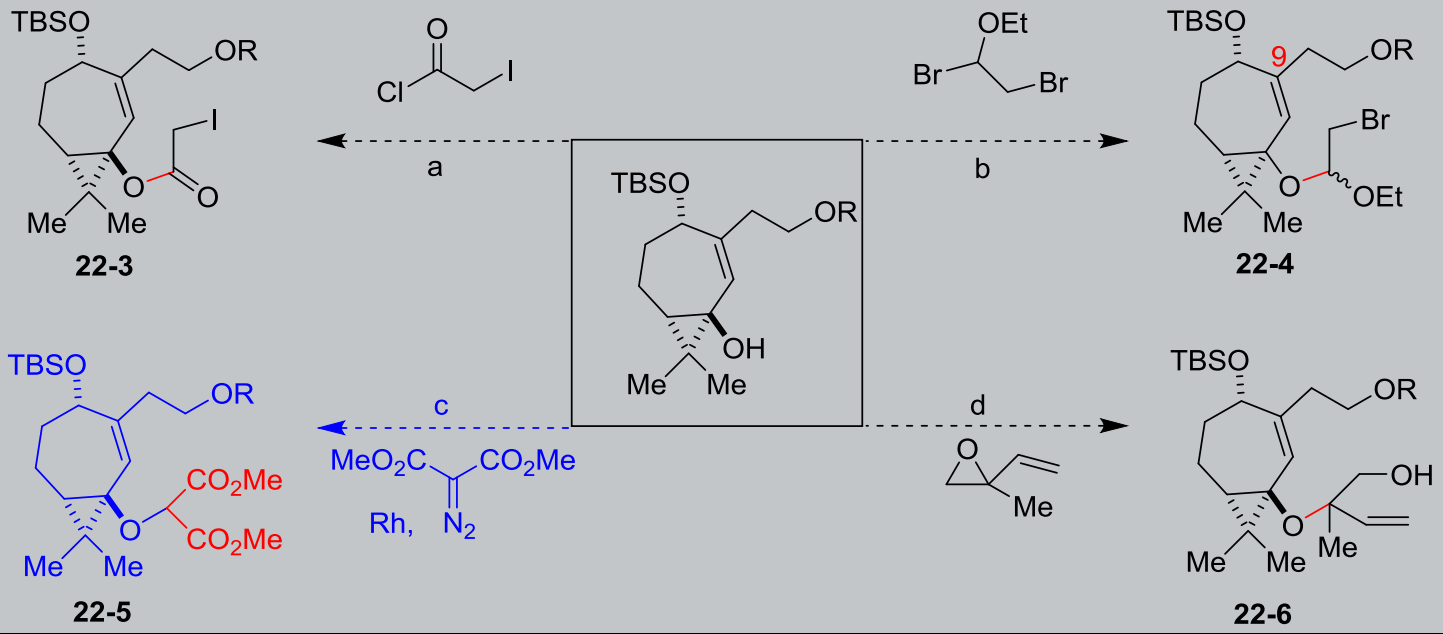




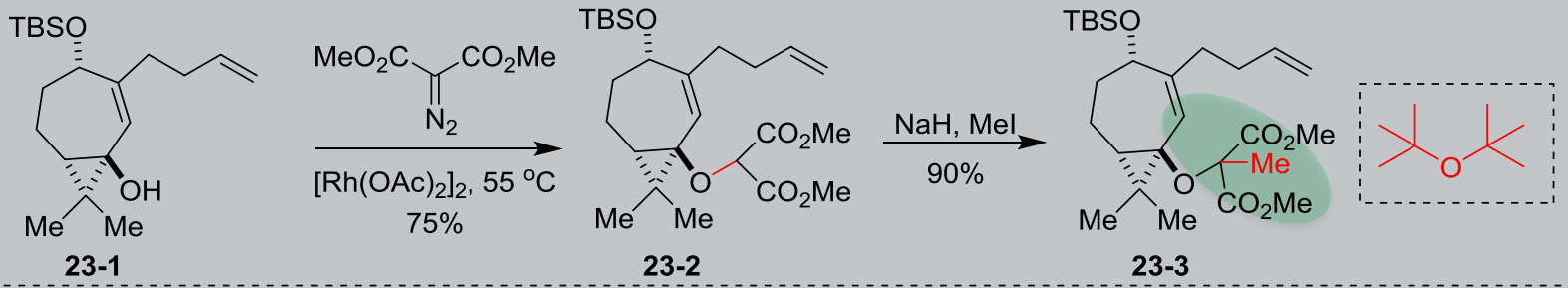


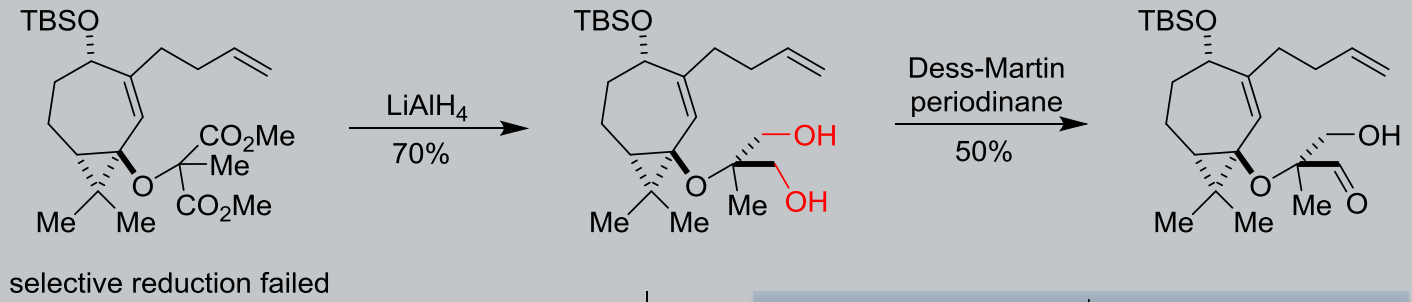
Revised Strategy based on [3,7] bicycle



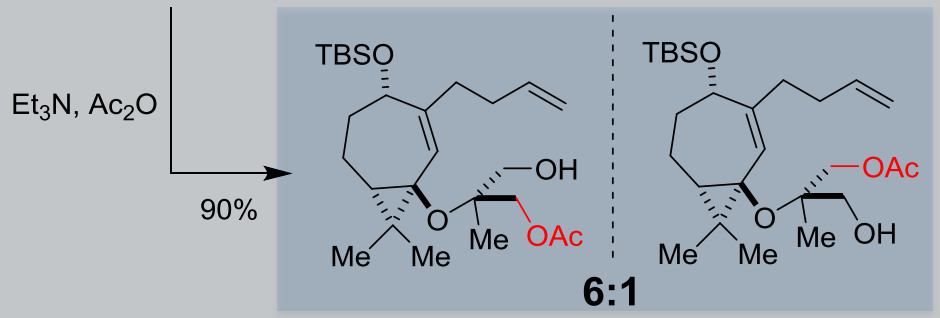


Rh-catalyzed O–H bond insertion





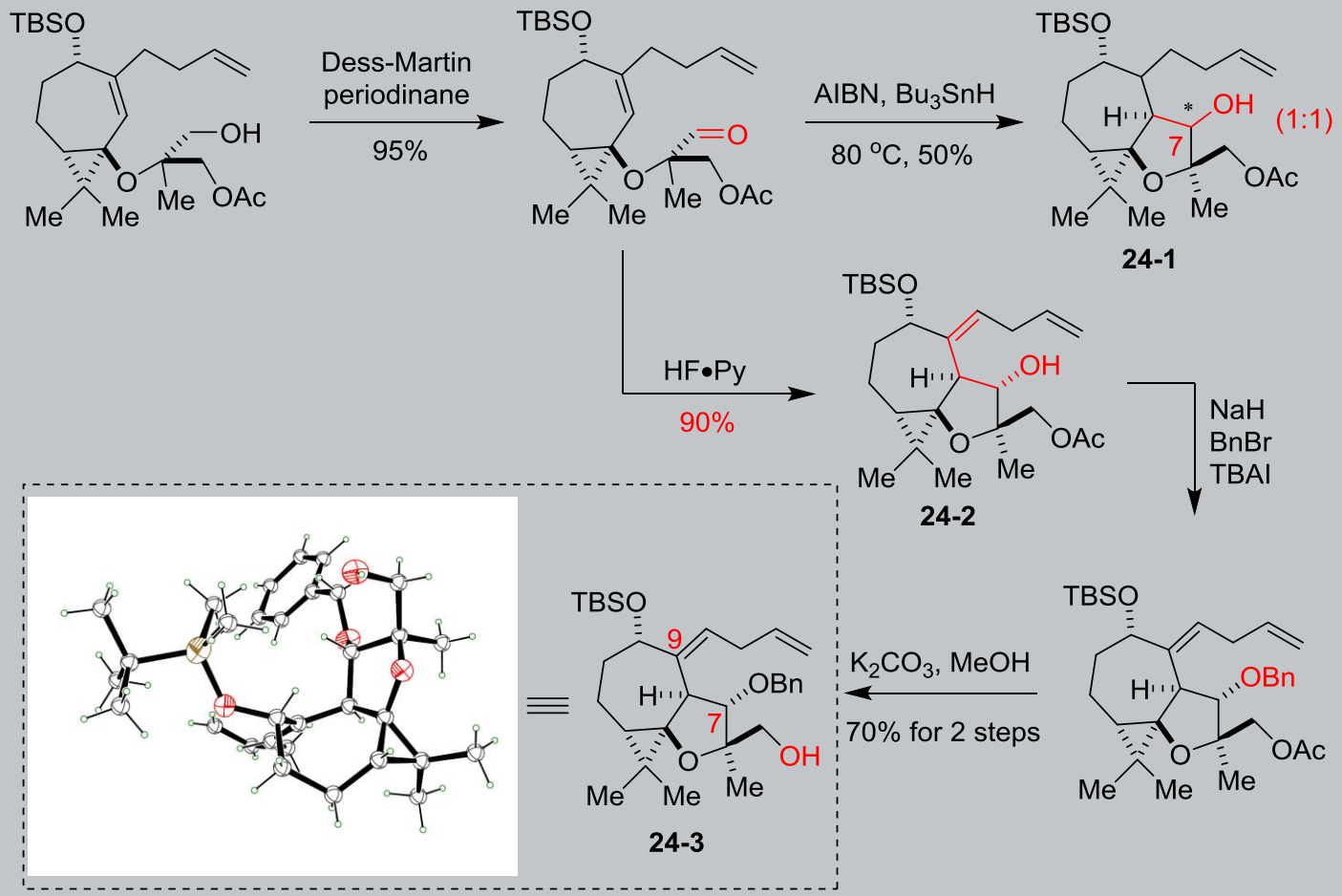
selective reduction failed



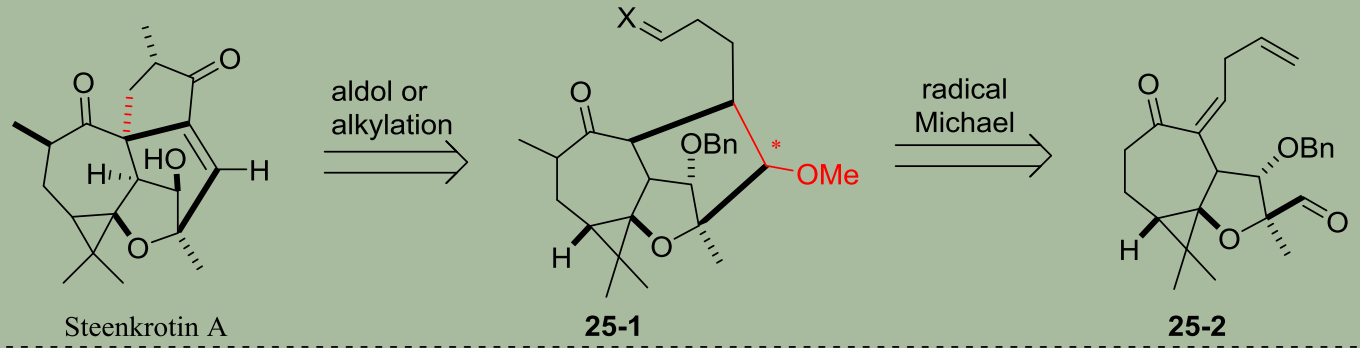
[TMS, TBS, Ts,] failed(3:2)

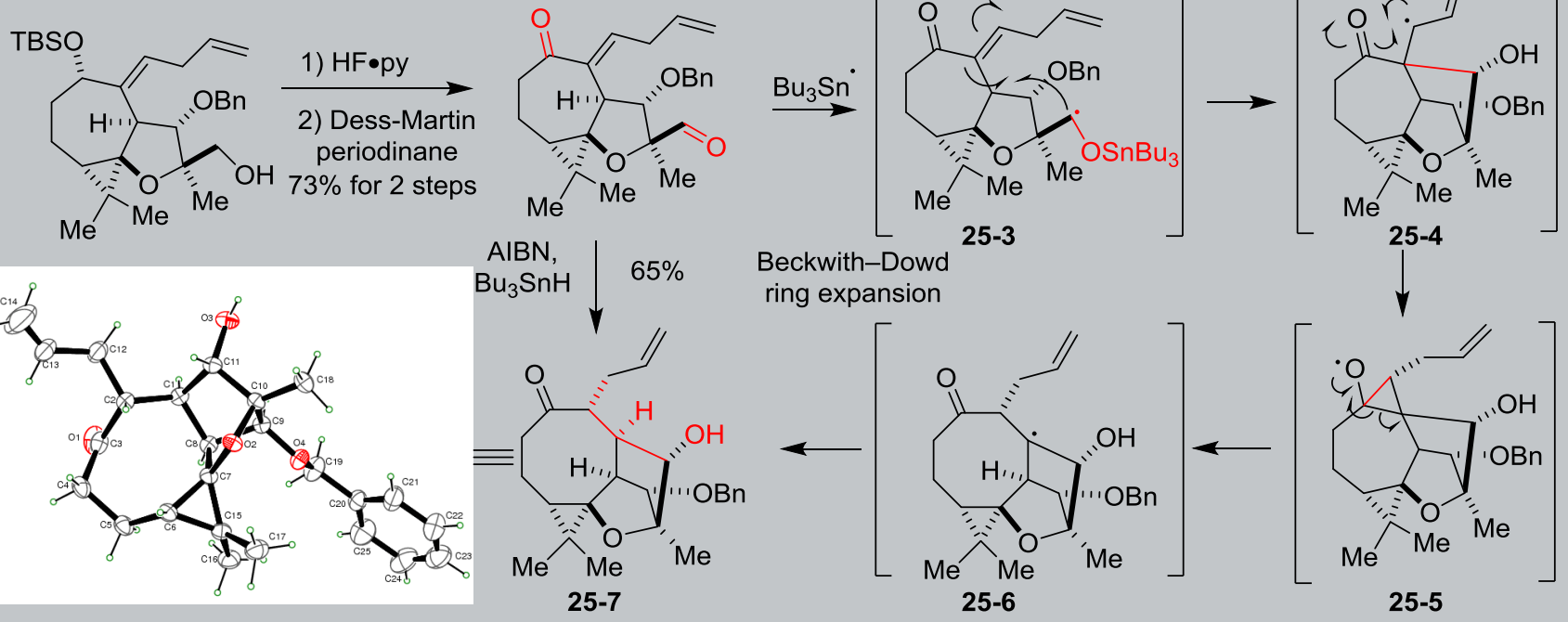
selective protection

Carbonyl-ene construct [3,5,7] tricycle skeleton

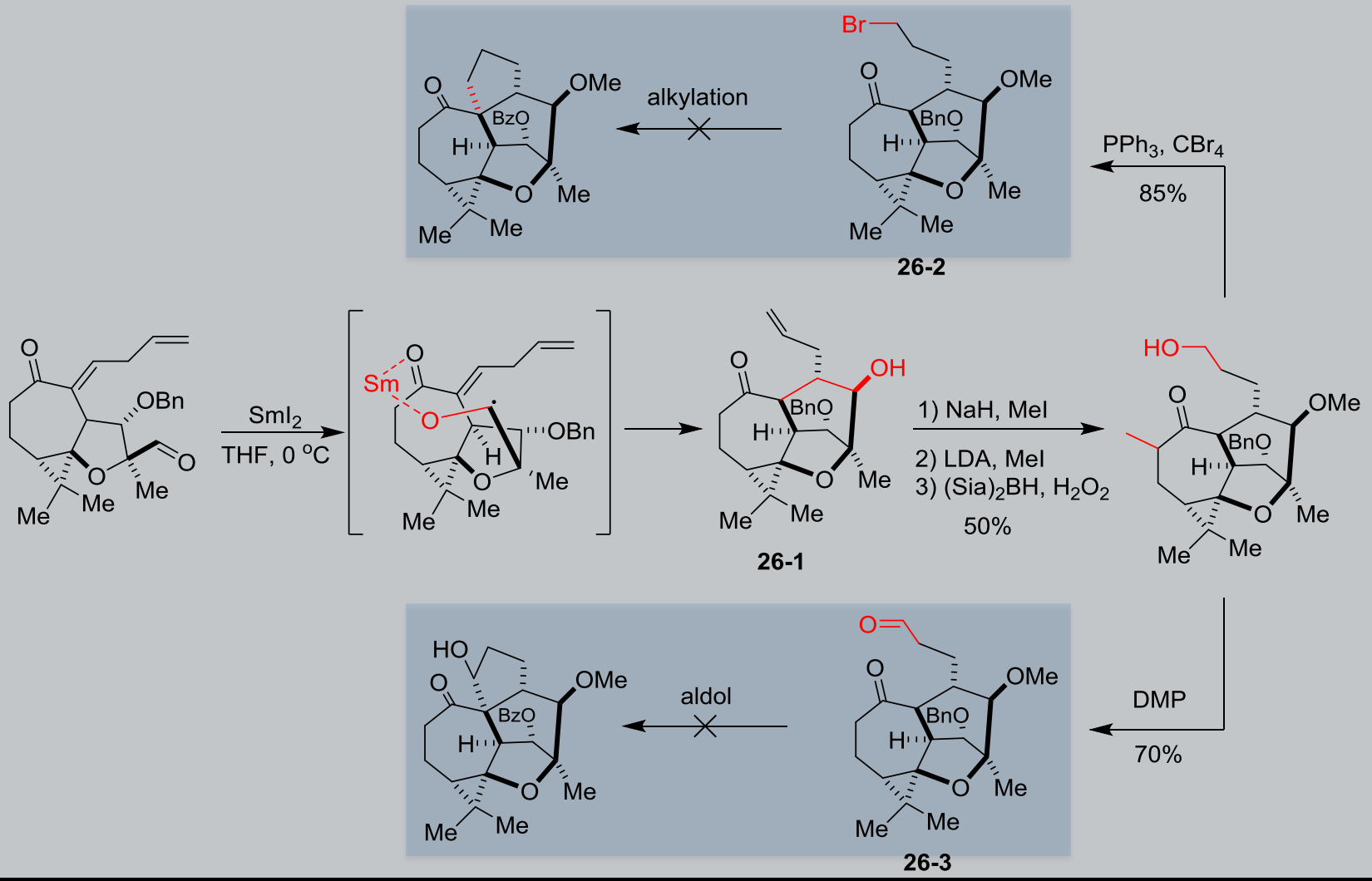


The Unexpected formation of [3,5,6,8] tetracycle

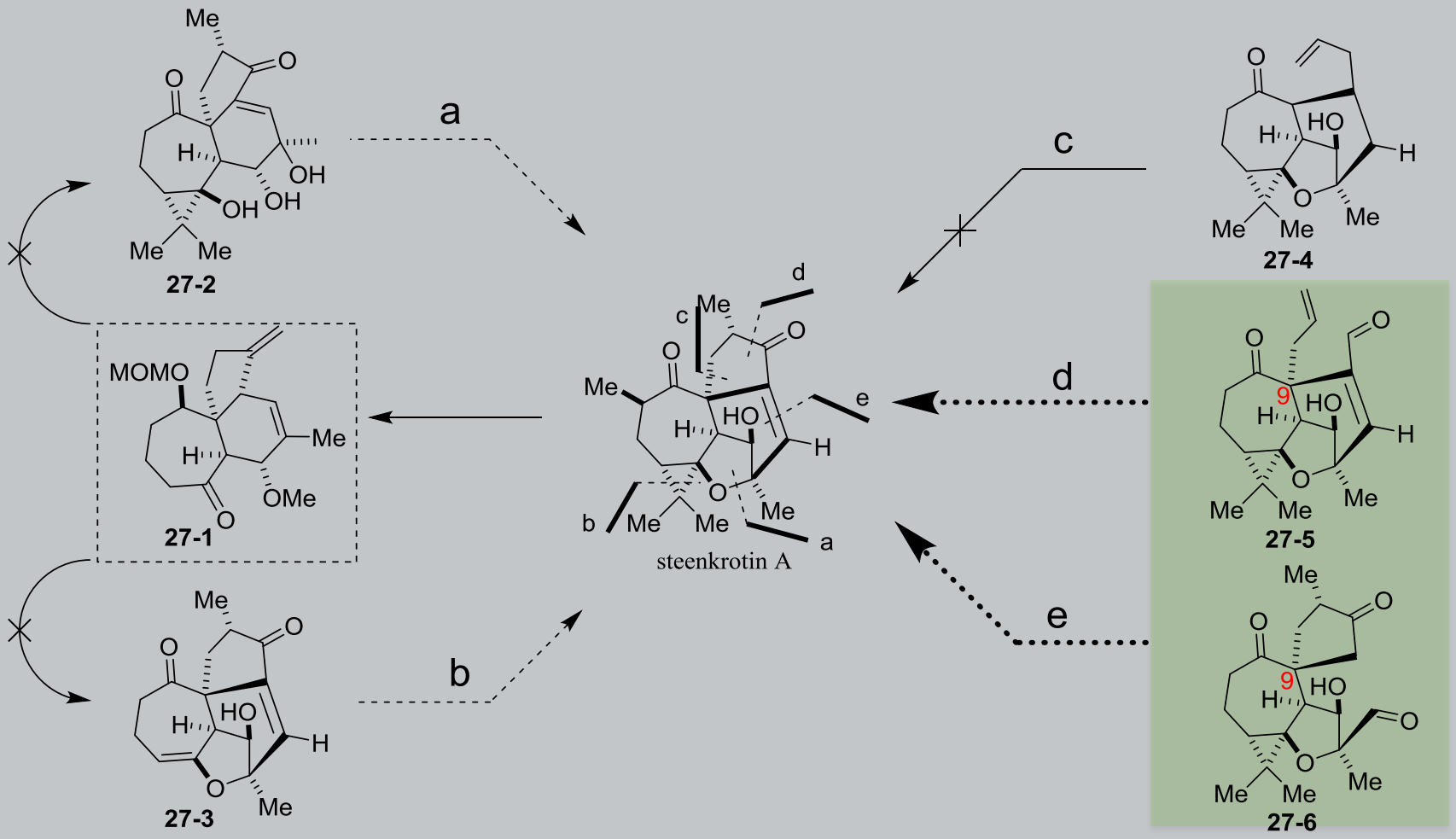




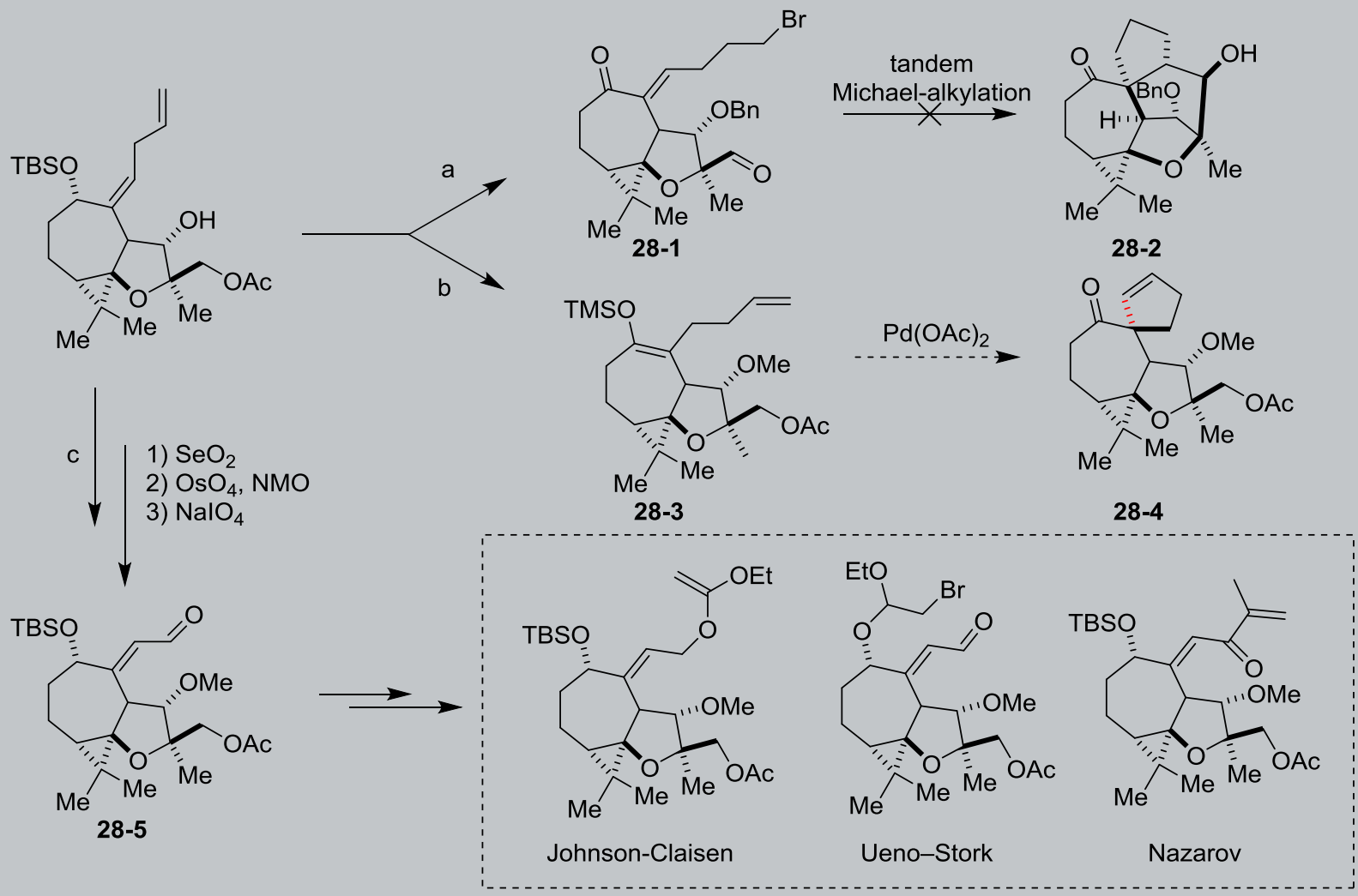
Synthesis of [3,5,6,7] tetracycle via SmI_2 mediated cyclization



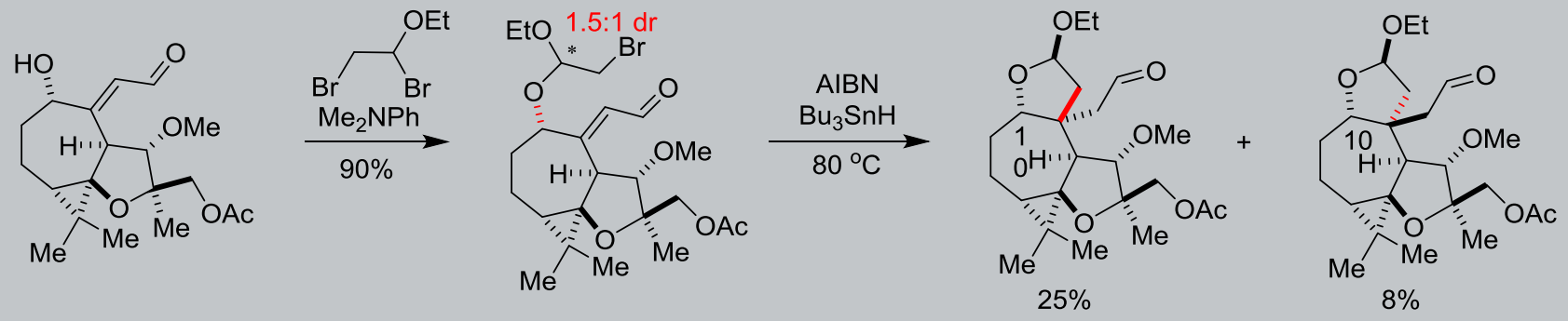
Retrosynthetic analysis of steenkrotin A

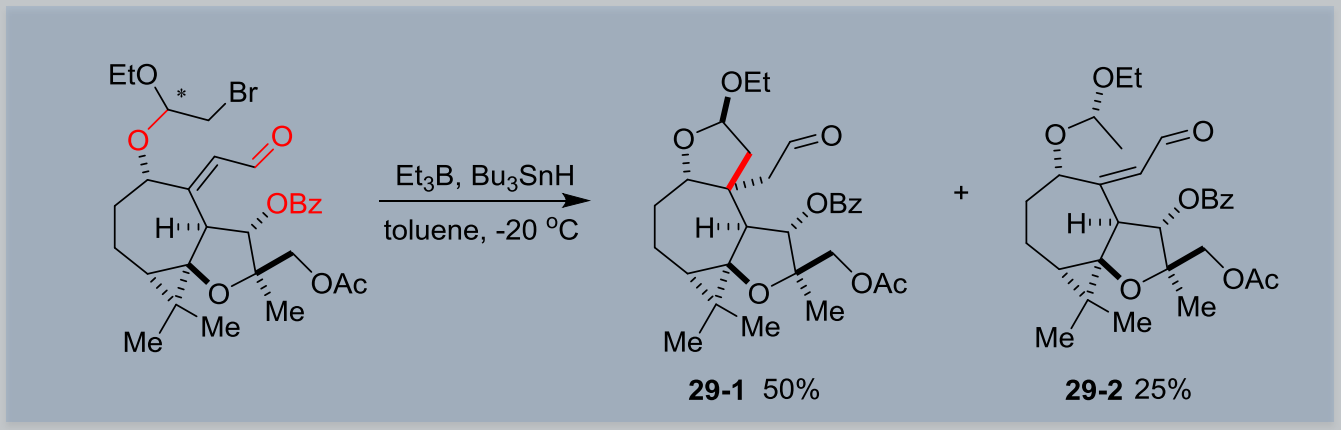


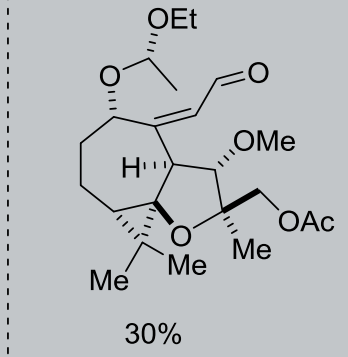
The last obstacle------- **Quaternary Center**



Conquer the **Quaternary Center**

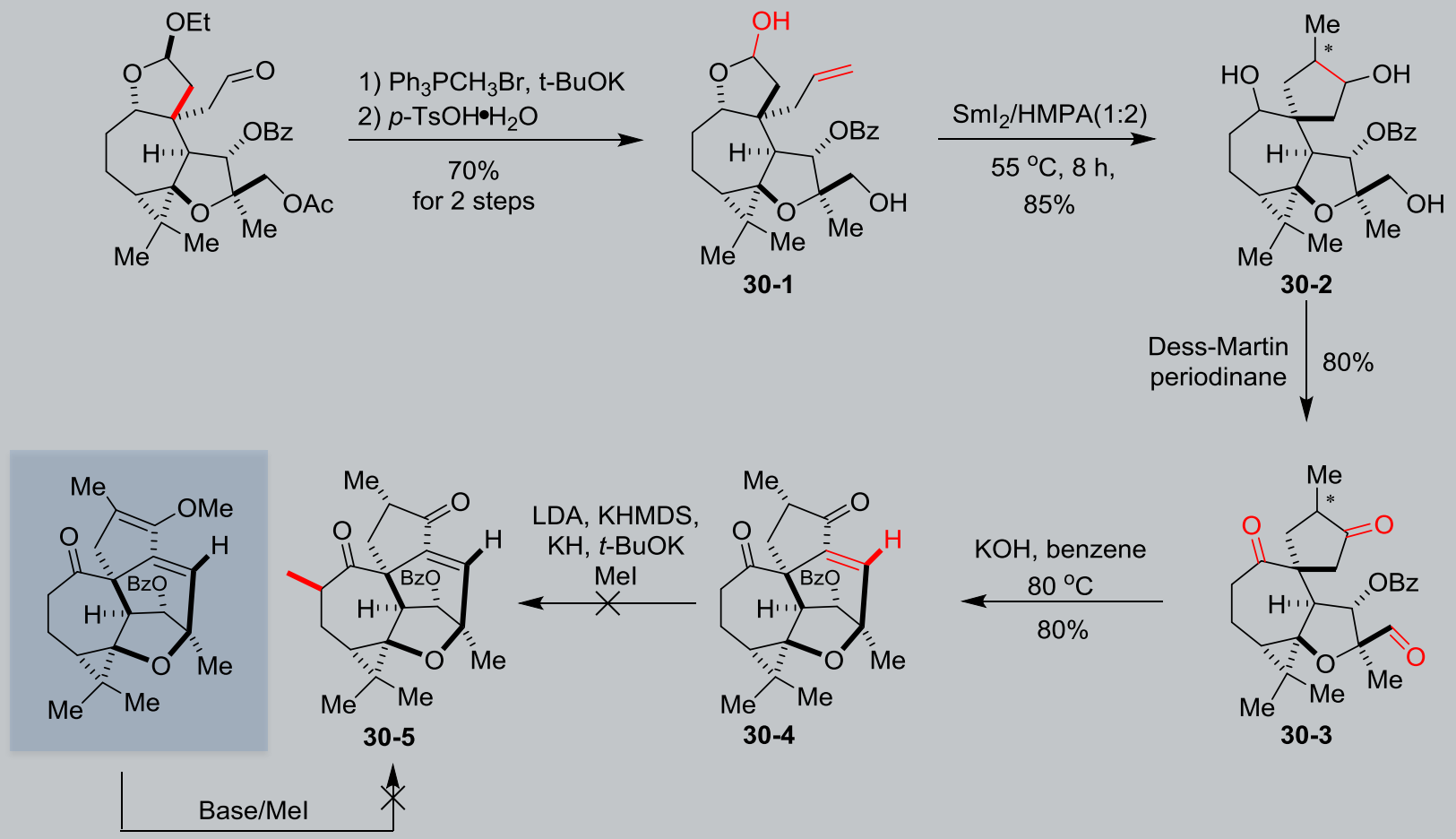




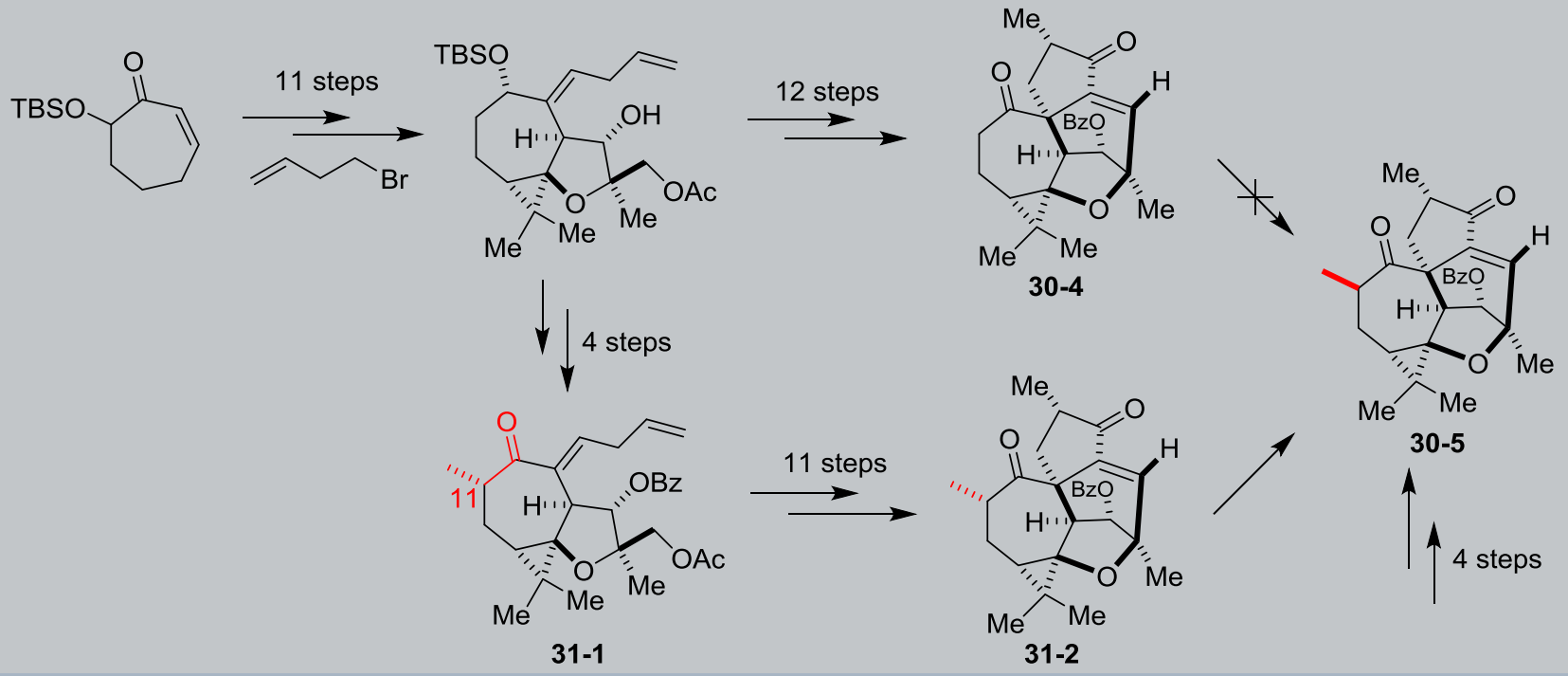


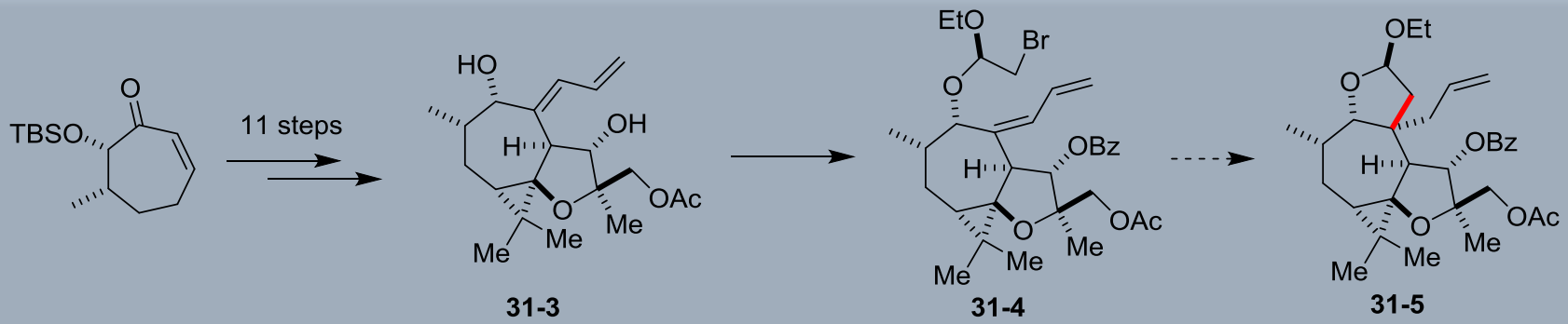
After the successful establish the **Quaternary Center,**
we full of confidence to finish the total synthesis of the molecule!

Synthesis [3,5,5,6,7] pentacycle of steenkrotin A

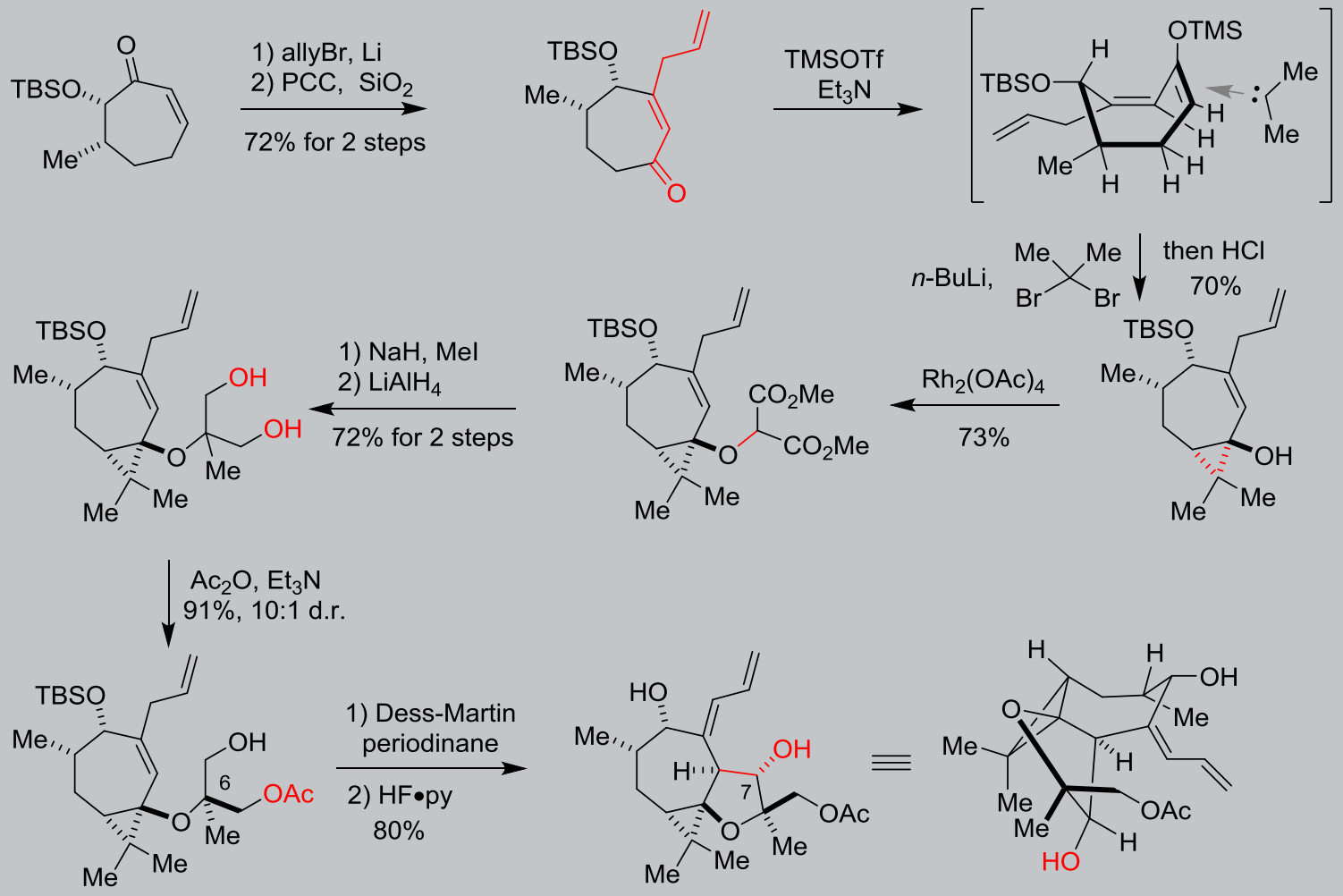


Optimization! Shorten the steps!

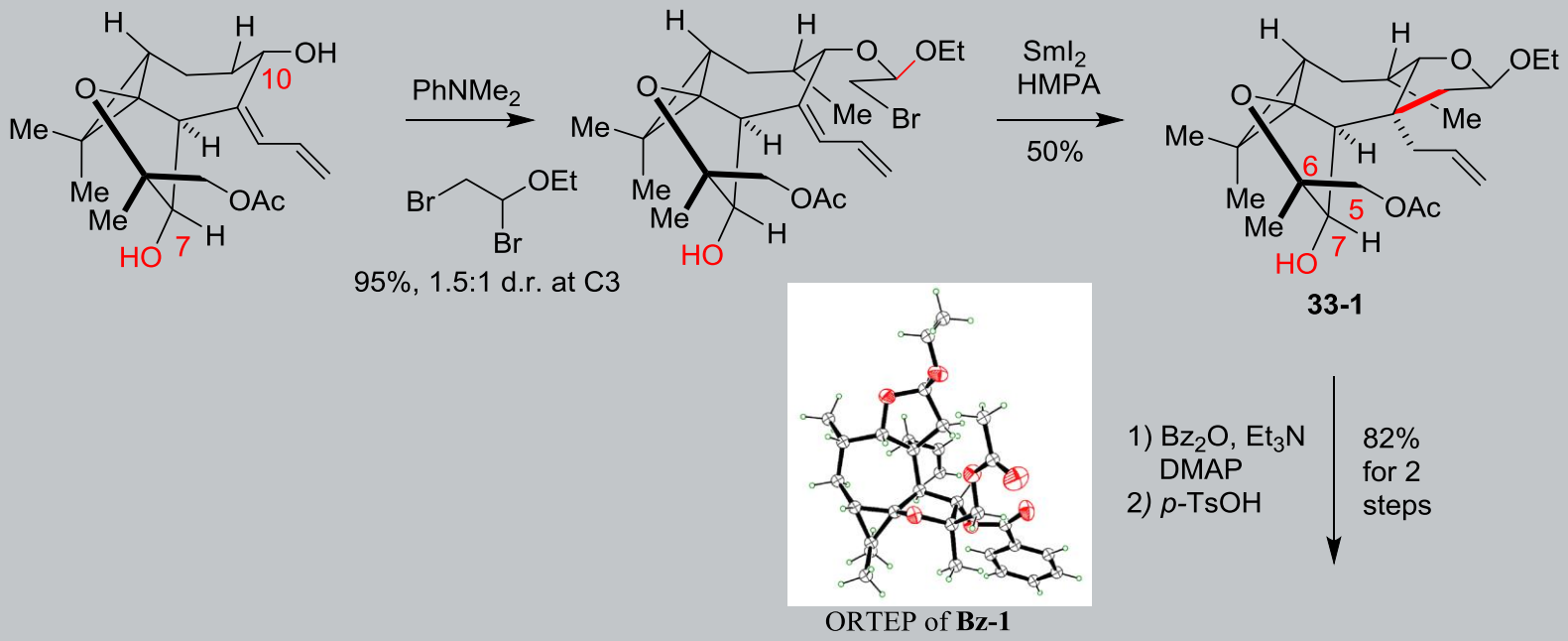




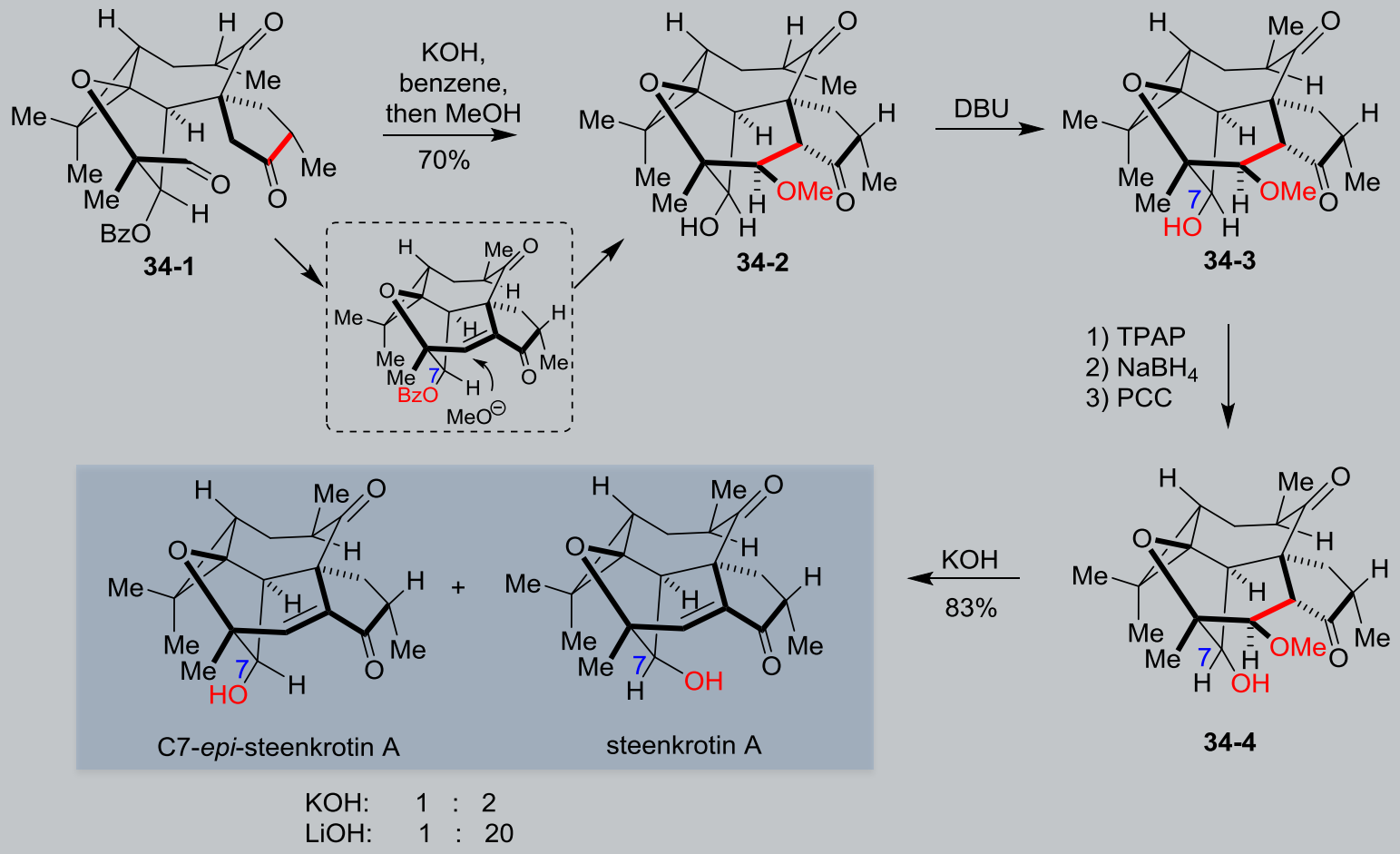
Synthesis of the Ueno–Stork precursor



Synthesis of [3,5,5,7] tetracycle

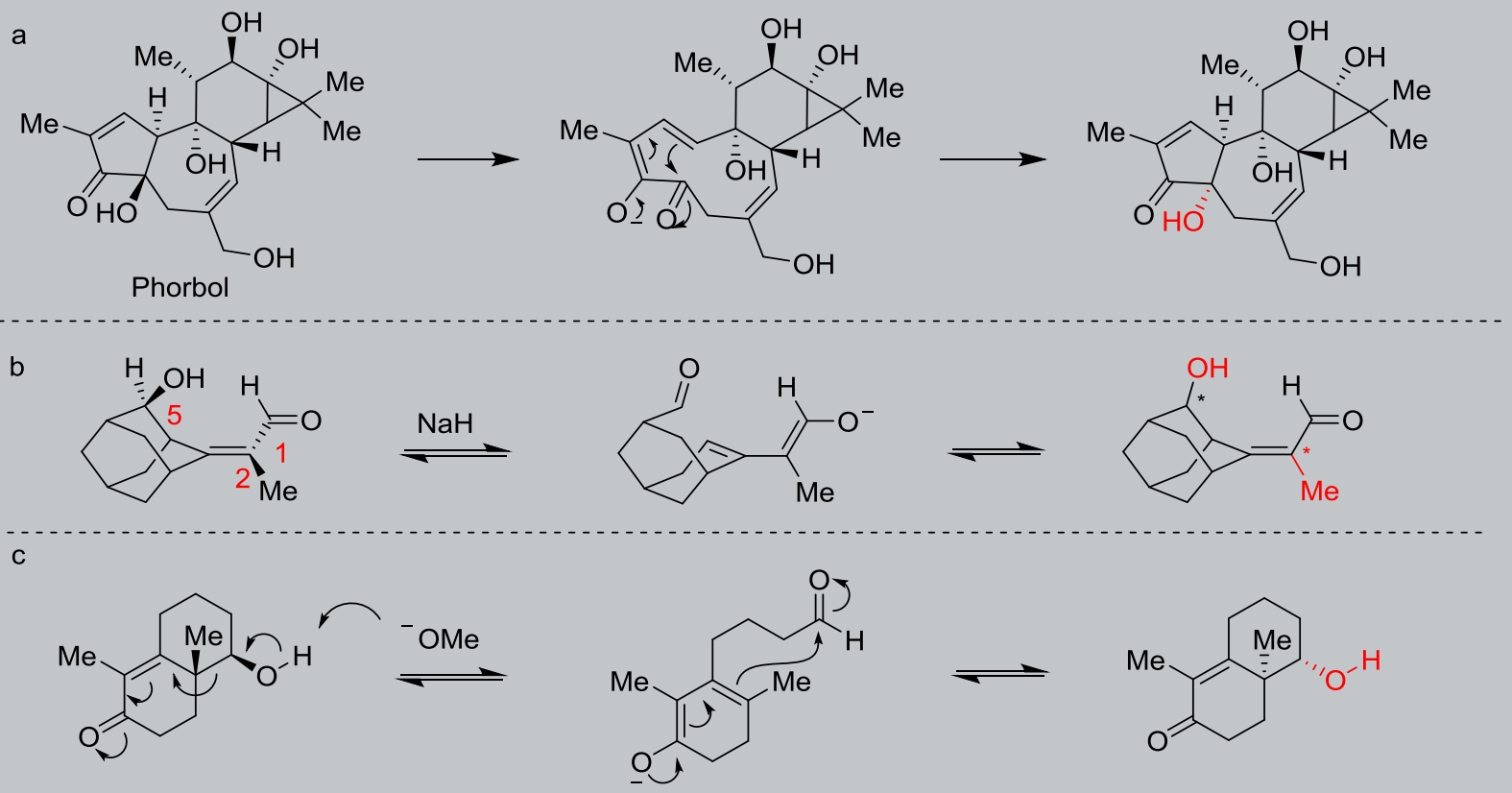


Total Synthesis of Steenkrotin A



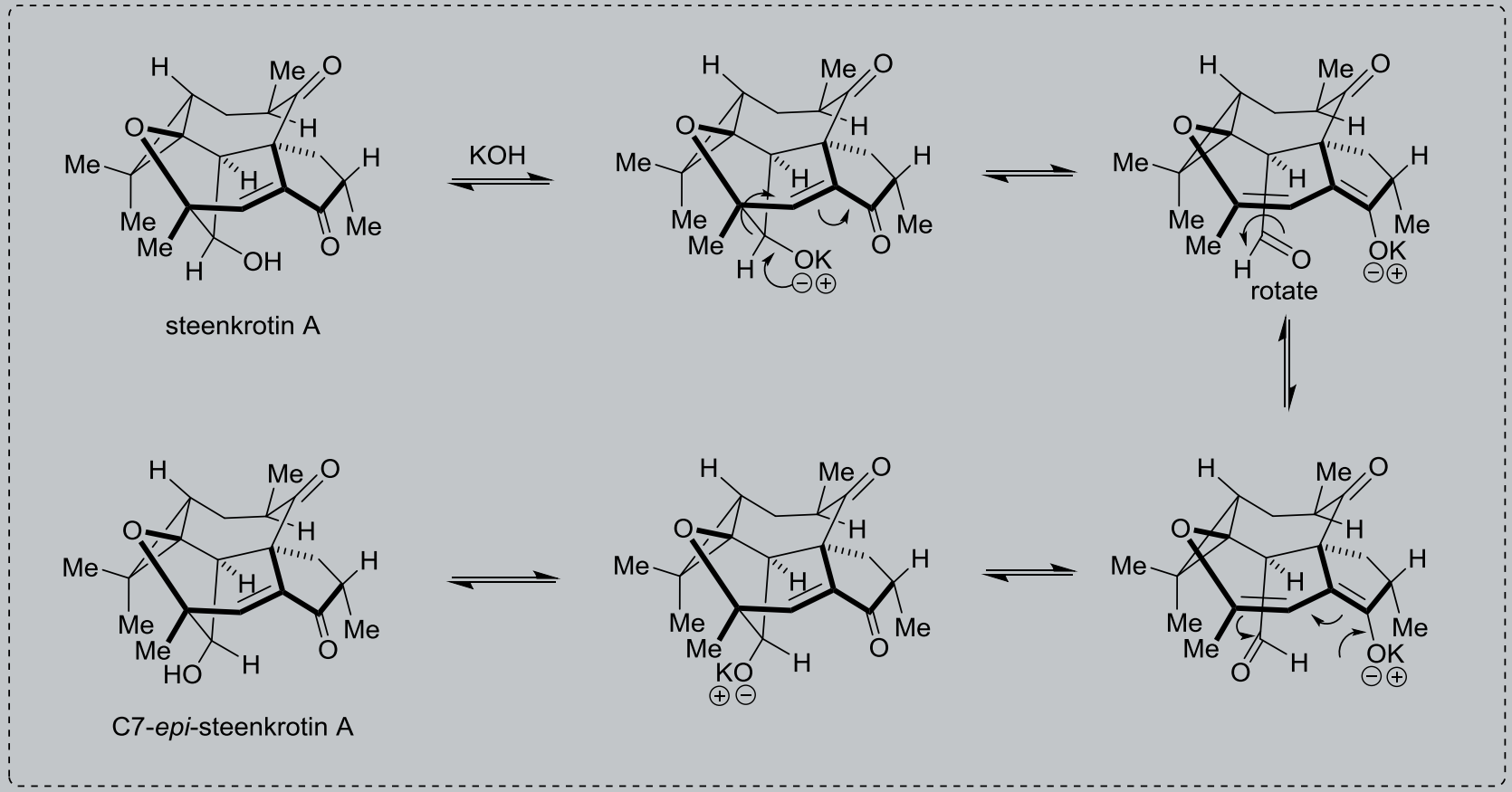
(1) Saiyong Pan,† Jun Xuan,† Beiling Gao, An Zhu, Hanfeng Ding.* *Angew. Chem. Int. Ed.* **2015**, *54*, 6905-6908
(†S.P. and J.X. contributed equally)

Cascade vinylogous–retro aldol/aldol reaction

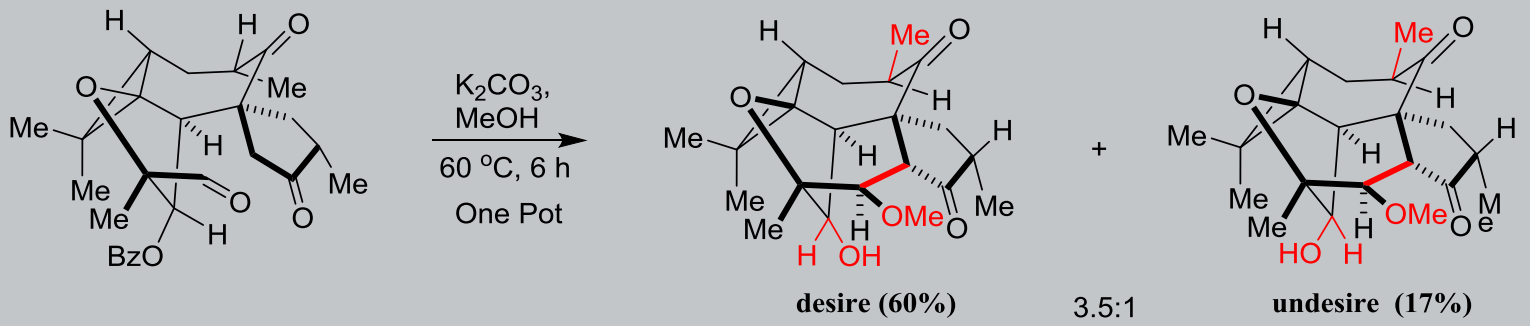


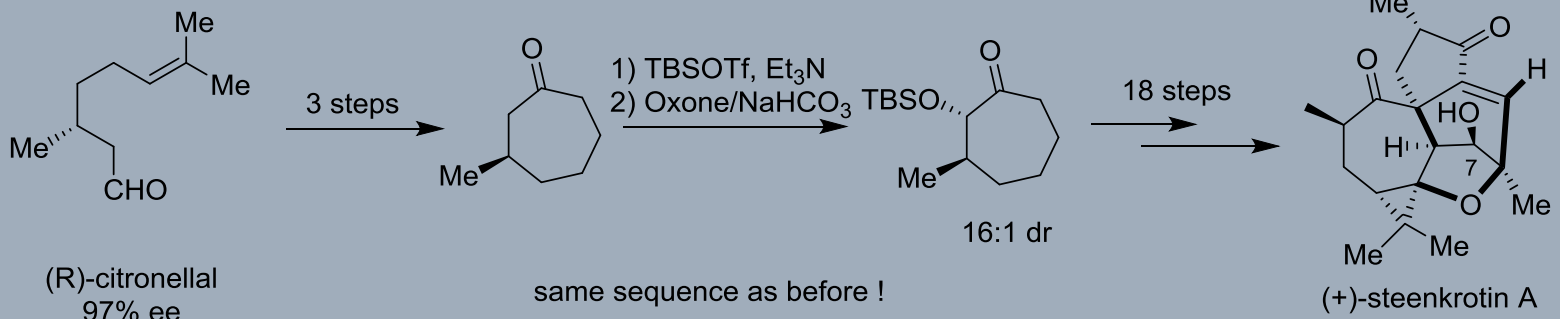
(1) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.
(2) Walborsky, H. M.; Reddy, S. M. J. Org. Chem. **1988**, 53, 4851.
(3) Payette, J. N.; Honda, T.; Yoshizawa, H.; Favaloro, F. G.; Gribble, G. W. J. Org. Chem. **2006**, 71, 416.

Cascade vinylogous–retro aldol/aldol reaction



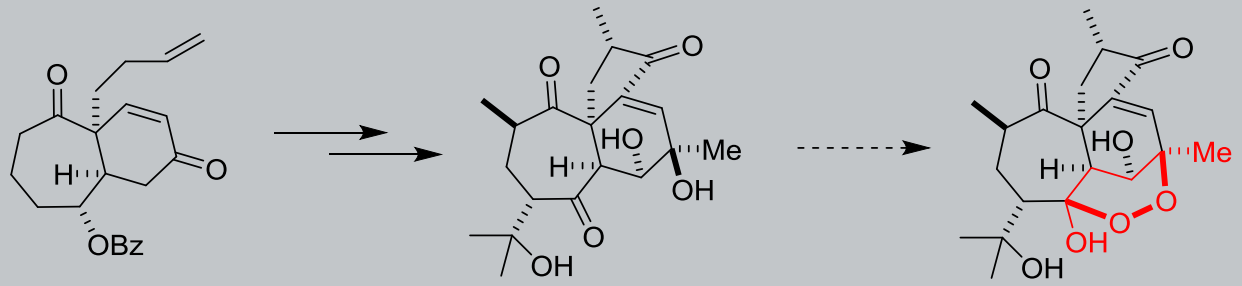
Enantioselective Total Synthesis of (+)-Steenkrotin A



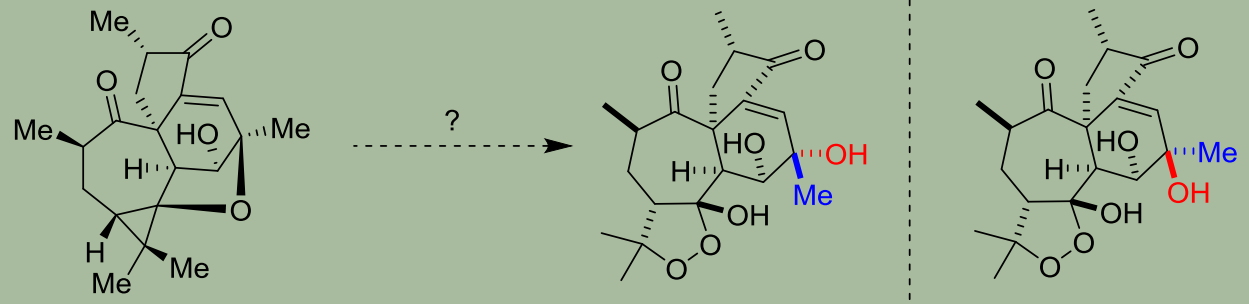


(1) Saiyong Pan,† Beiling Gao,† Jialei Hu, Jun Xuan, Hujun Xie, Hanfeng Ding.* *Chem. Eur. J.* **2015**, in press.
(†S.P. and B.G. contributed equally)

Perspective



steenkrotin B



which is real structure of steenkrotin B ?

Conclusions & Lessons

- Two Strategy was developed to synthesize [5,6,7] tricycle of steenkrotin A.
- First total synthesis of (+)-steenkrotin A was accomplished.
- The gem–dimethylcyclopropanol issue was discussed, and the valuable result can be a guide for similar synthesis.
- The quaternary centers and special moiety may better construct at the early stage of the synthesis.

THE END Thank you for attention!