

Literature Report 3

Total Synthesis of Aplydactone

Reporter: Xiao-Yong Zhai

Checker: Ji Zhou

Date: 2017-07-31

Liu, C.-G.; Chen, R.-Z.; Shen, Y.; Liang, Z.-H.; Hua, Y.-H.; Zhang, Y.-D.
Angew. Chem. Int. Ed. **2017**, *56*, 8187.

CV of Yandong Zhang



Yandong Zhang

Education:

- ❑ 1994–1998 B.S., Beijing Institute of Technology
- ❑ 1998–1999 Research assistant, Institute of Chemistry
- ❑ 1999–2002 M.S., Peking University (Jiahua Chen)
- ❑ 2002–2004 Research assistant, Peking University (Zhen Yang)
- ❑ 2004–2008 Ph.D., Peking University (Zhen Yang)
- ❑ 2008–2010 Postdoc., Columbia University (Prof. Danishefsky)
- ❑ 2011–2017 Associate Professor, Xiamen University

Research:

- Stereoselective reactions with relevance to both natural products and medicinal chemistry.
- New strategies for the synthesis of terpenoid natural and unnatural products.
- Therapeutic anti-cancer/anti-HBV agent with natural products as lead compounds.

Contents

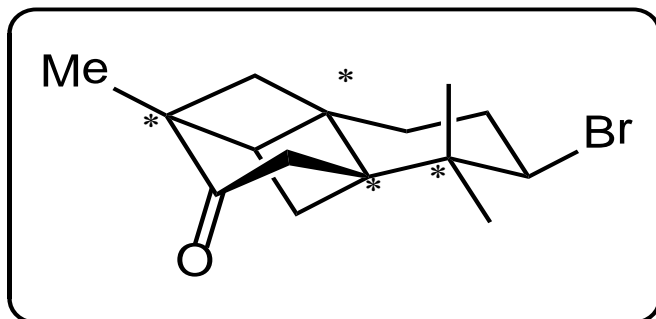
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3 Total Synthesis of Aplydactone by Yandong Zhang

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Introduction



Aplydactone



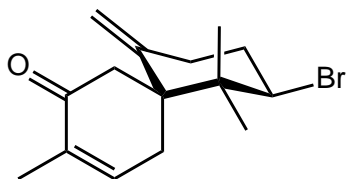
Aplysia dactylomela
(黑指纹海兔)

- Isolated from the *Aplysia dactylomela* in 2001;
- A highly strained tetracyclic framework consisting of two six-membered rings and a [2]-ladderane system ;
- The tetracycle also comprises four quaternary centers.

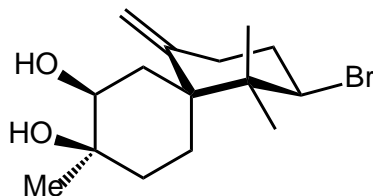
Stonik, V. A. *et al. J. Am. Chem. Soc.* **2001**, 123, 504.

Introduction

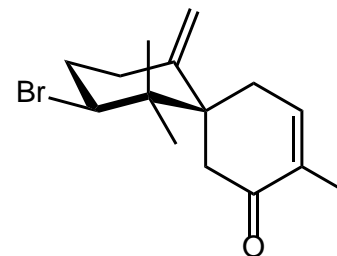
Natural products isolated from *Aplysia dactylomela*



Dactylone (1)

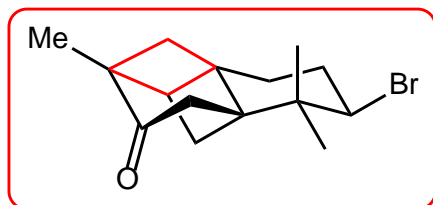


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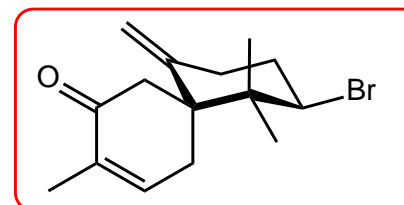
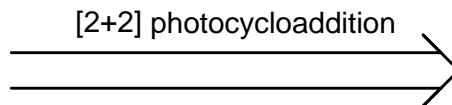


10-*epi*-Dactylone (3)

The biosynthetic relationship



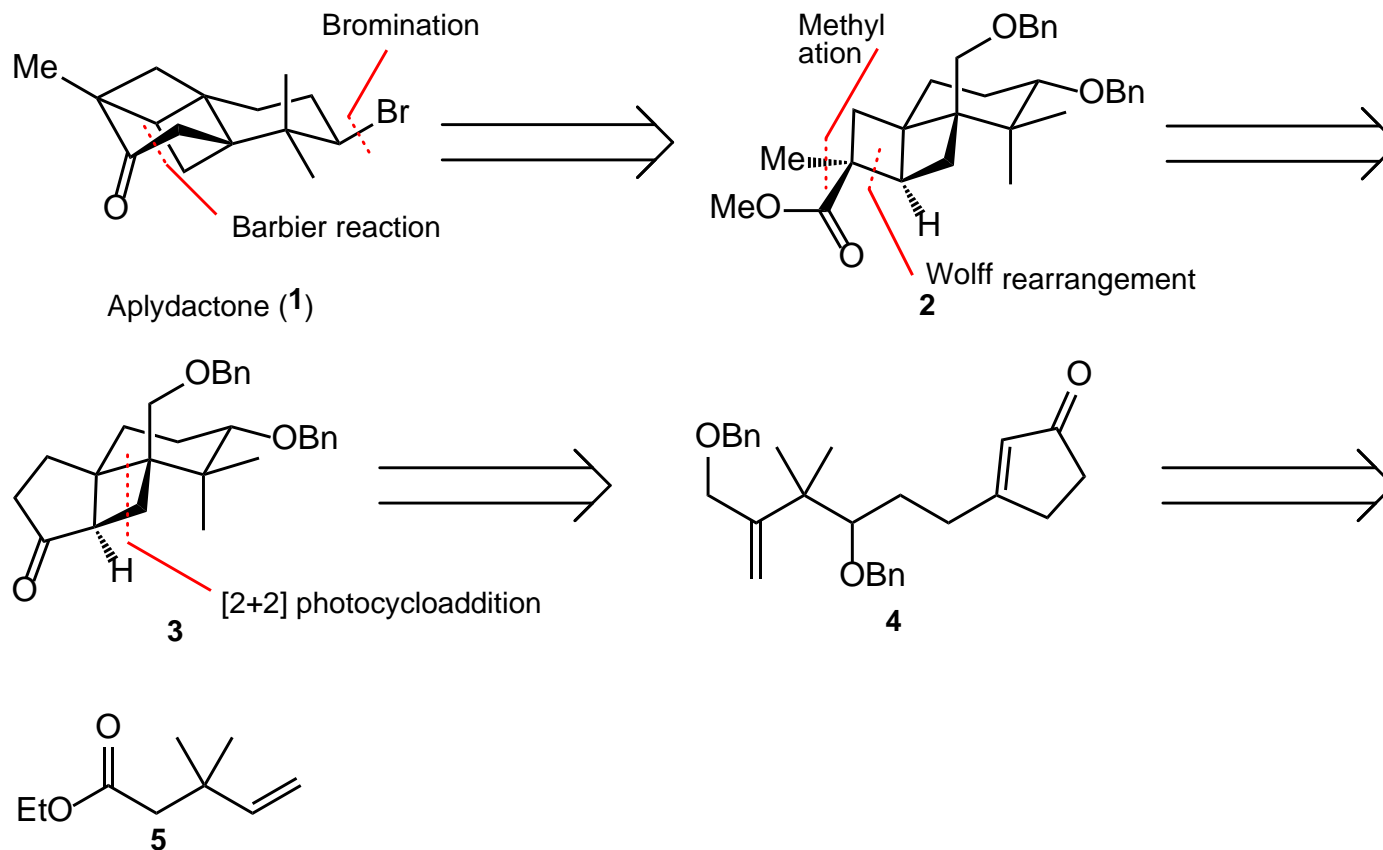
Aplydactone (4)



Dactylone (1)

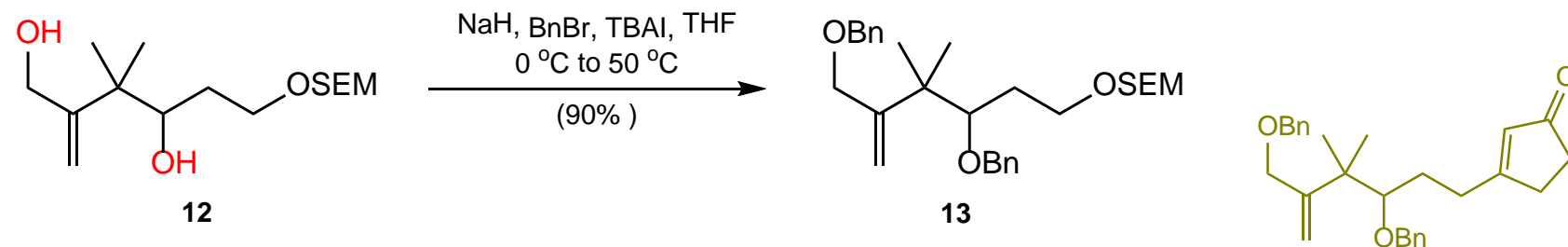
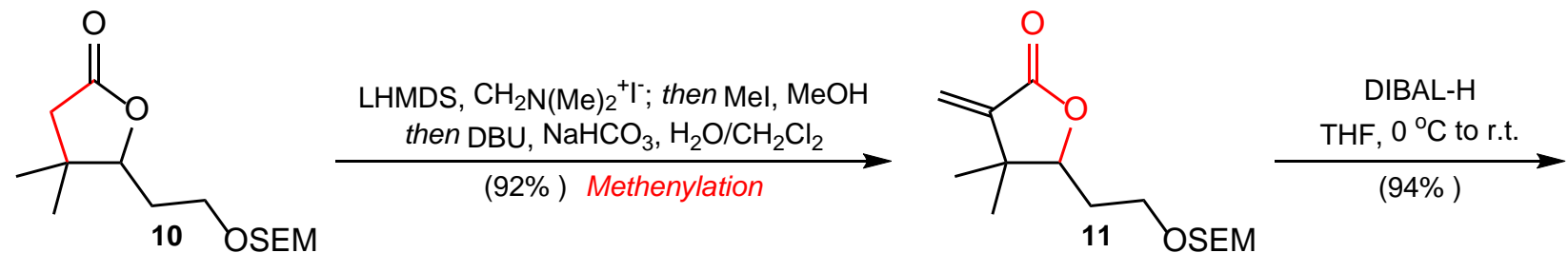
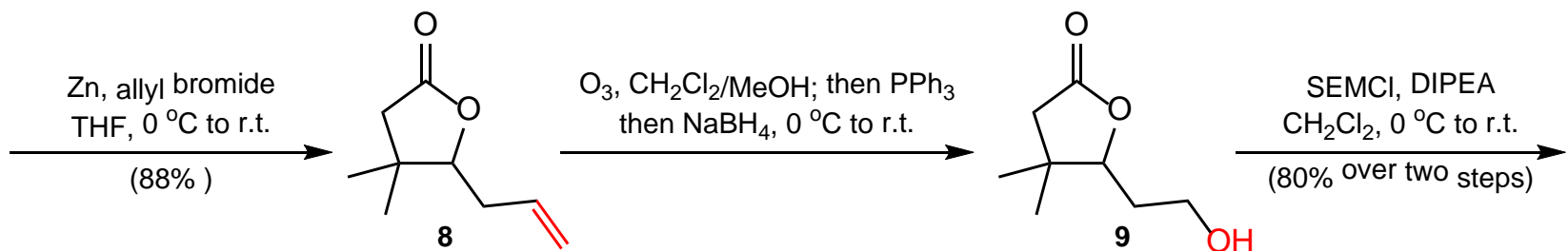
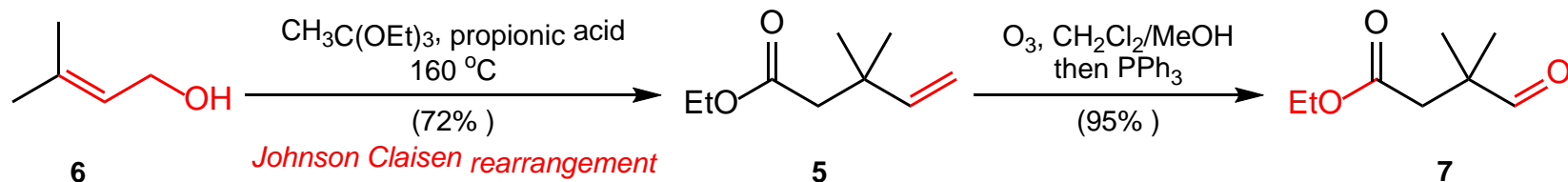
Stonik, V. A. *et al.* *J. Am. Chem. Soc.* **2001**, 123, 504.

Retrosynthetic analysis of Aplydactone

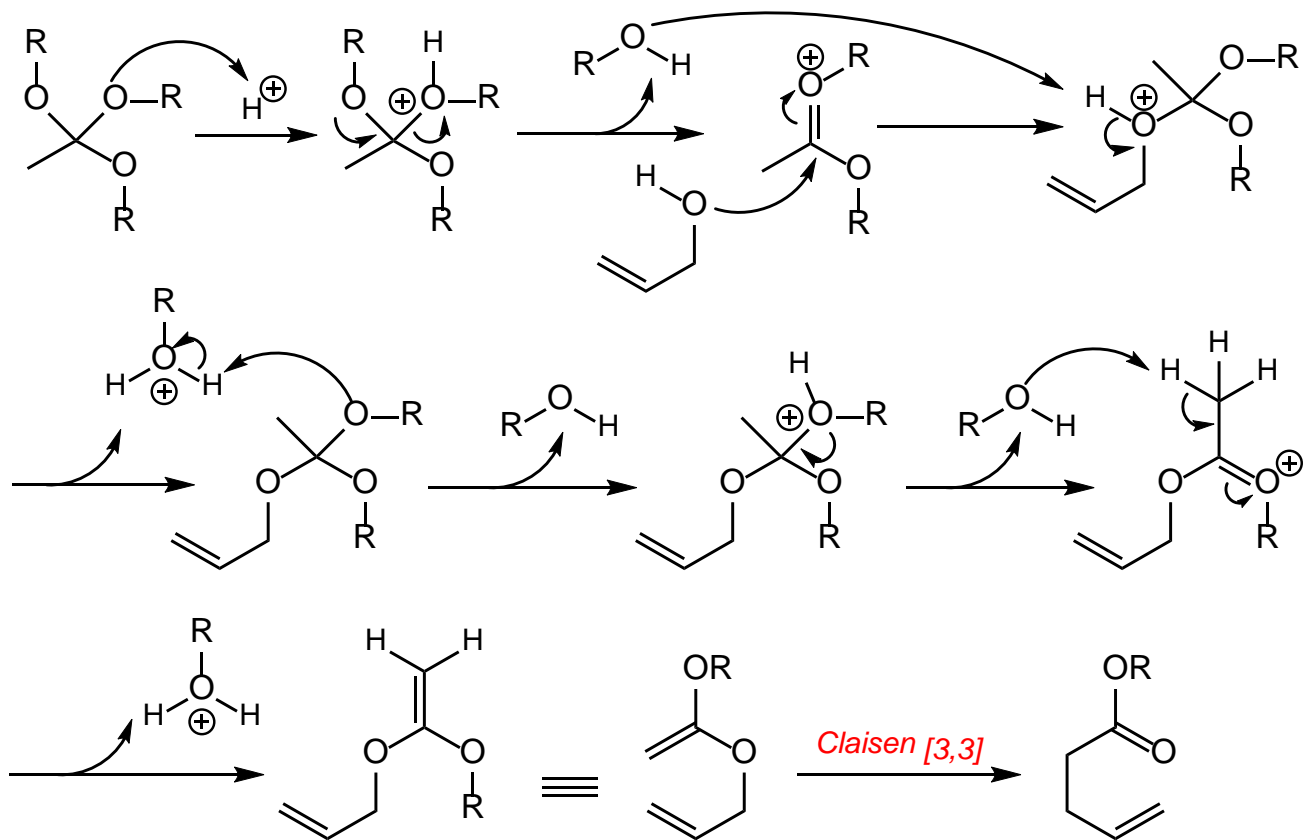
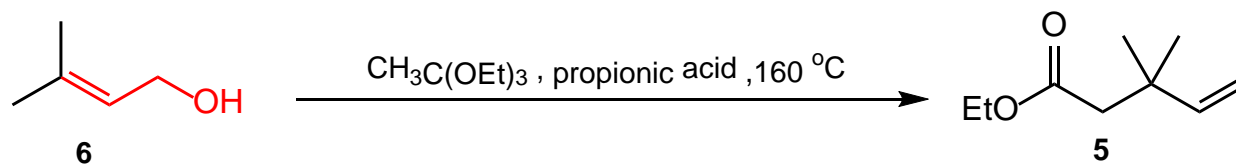


Trauner, D. *et al.* *Angew. Chem. Int. Ed.* **2016**, *55*, 11251.

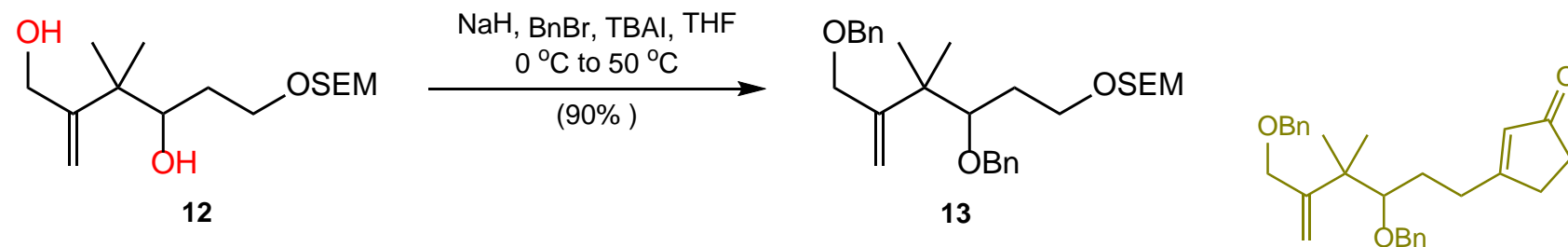
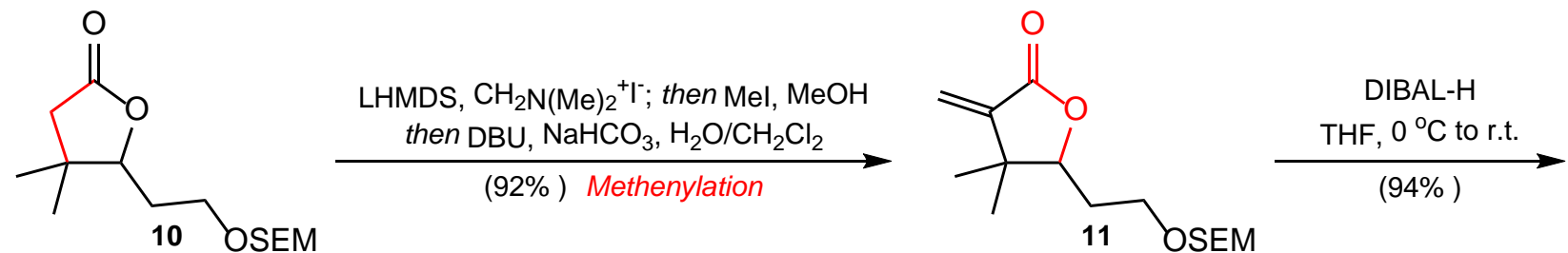
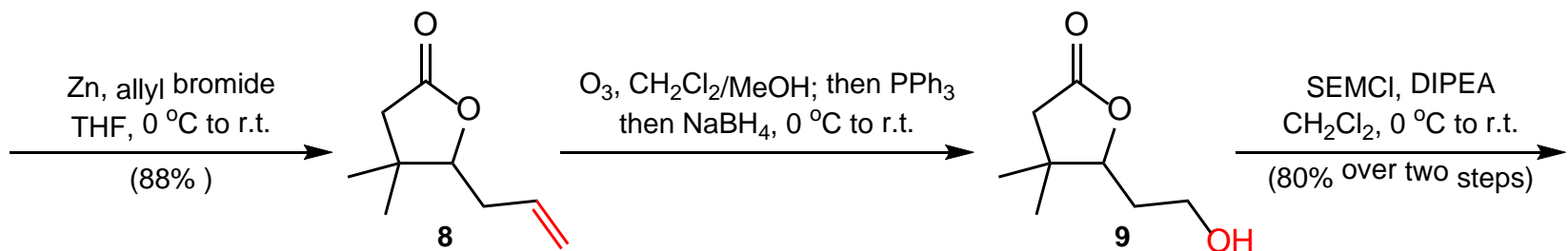
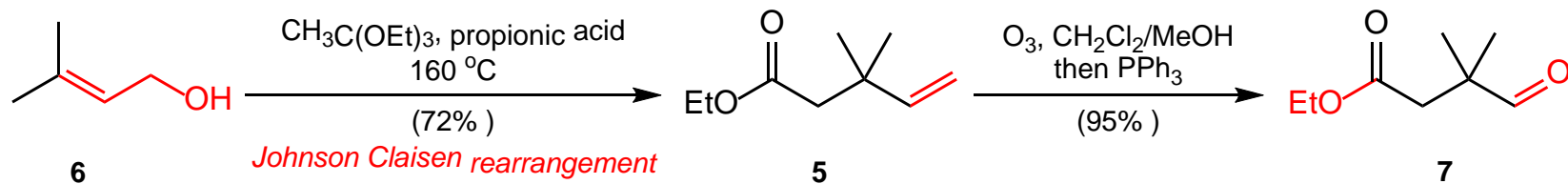
Total synthesis of Aplydactone



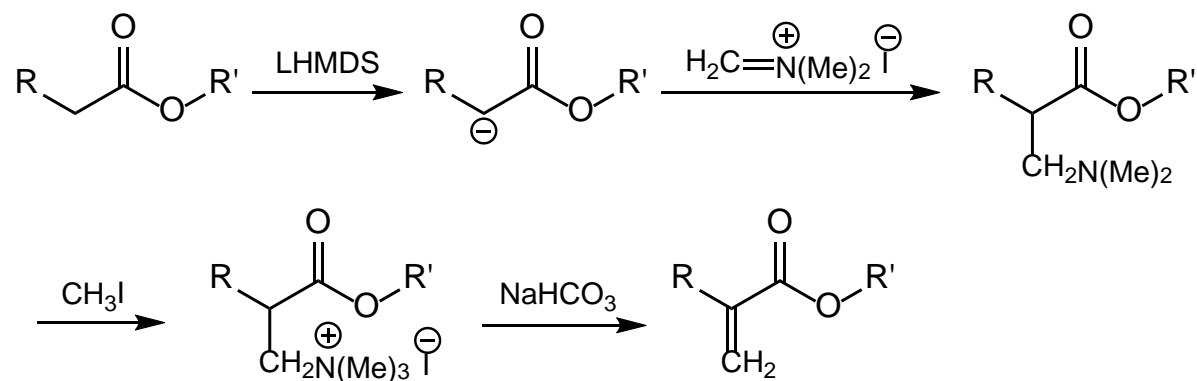
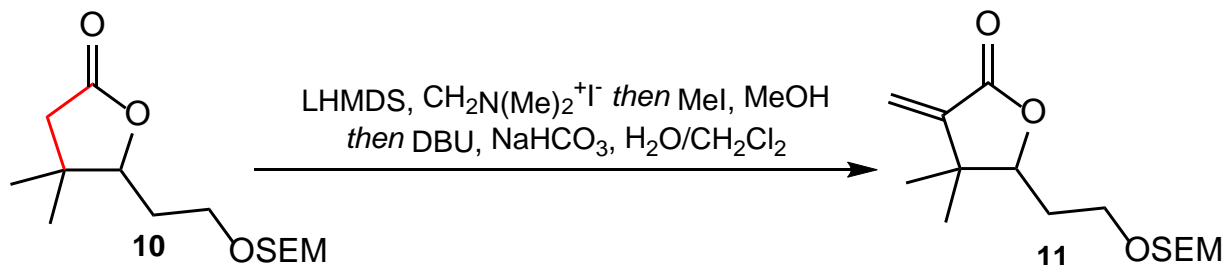
Johnson–Claisen rearrangement



Total synthesis of Aplydactone

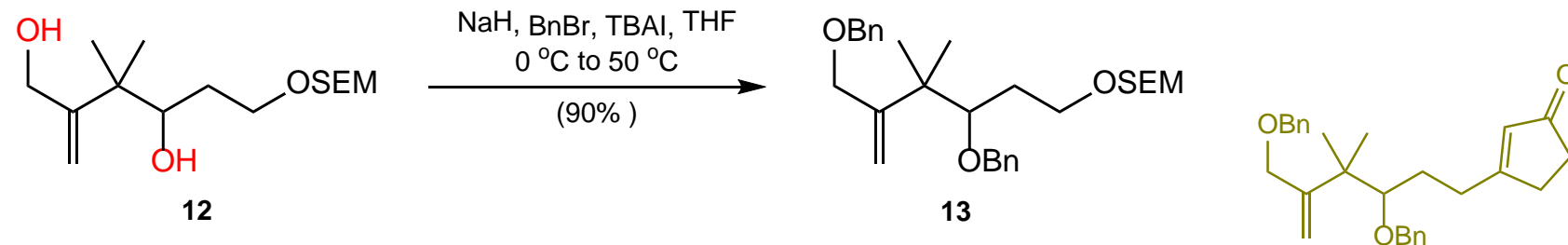
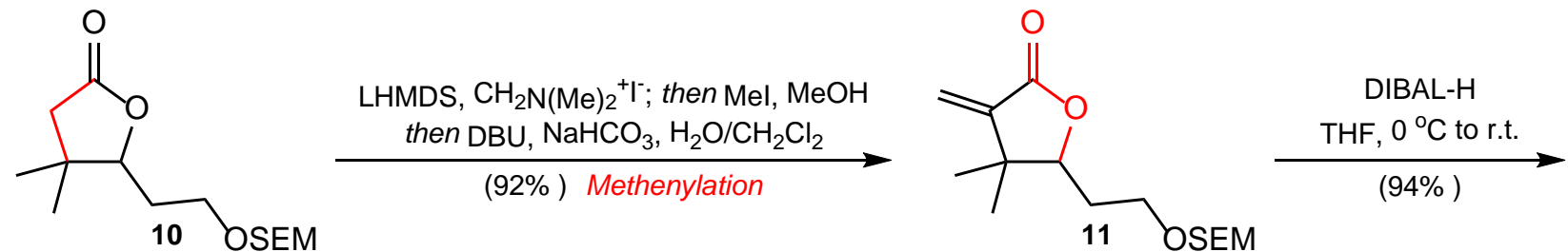
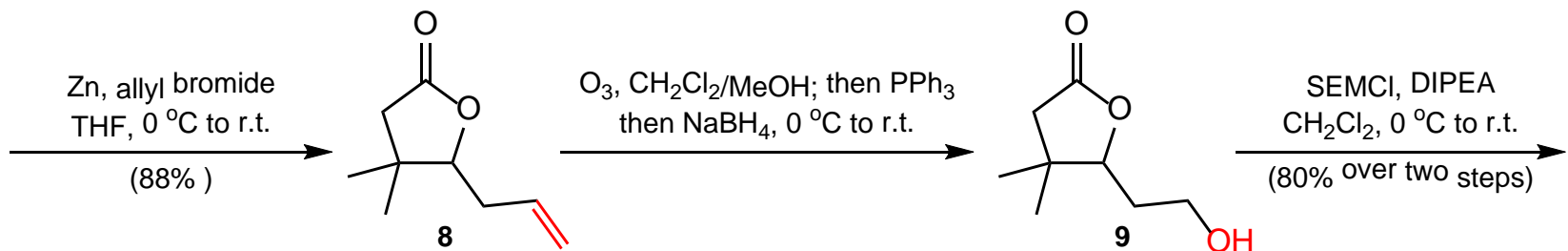
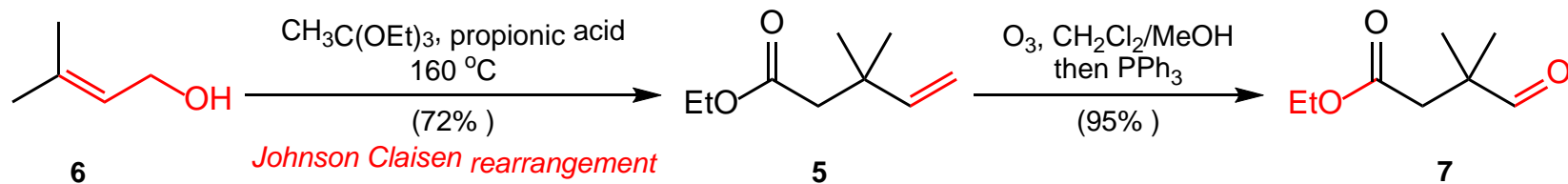


Methenylation of lactone 11

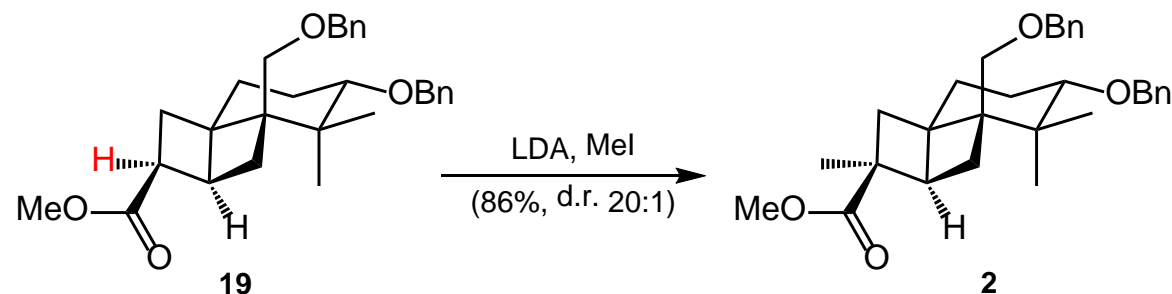
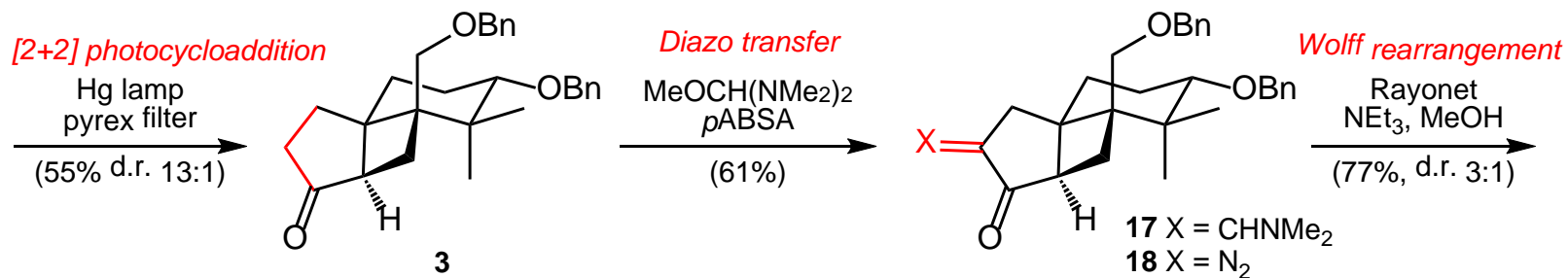
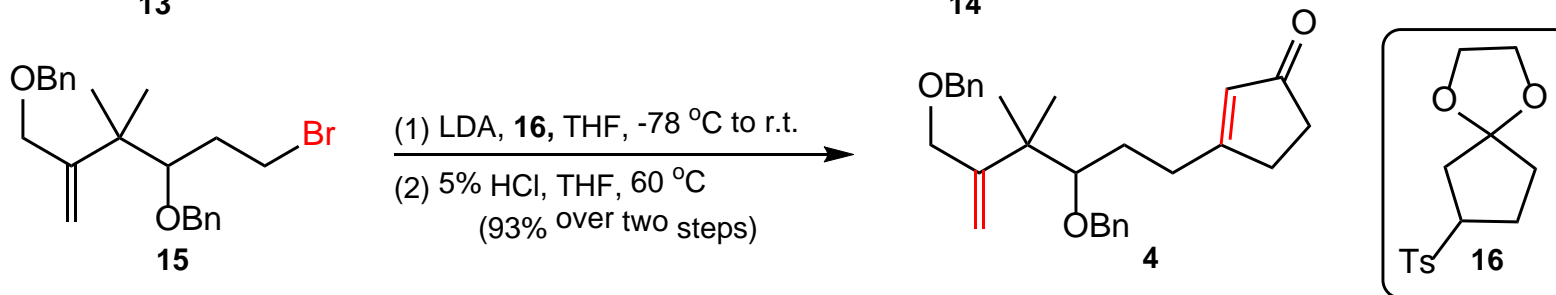
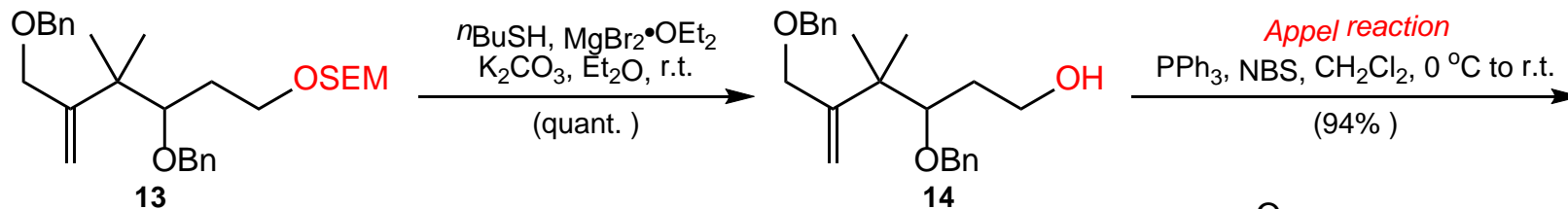


Poulter, C. D. *et al.* *Tetrahedron Lett.* **1977**, *18*, 1621.

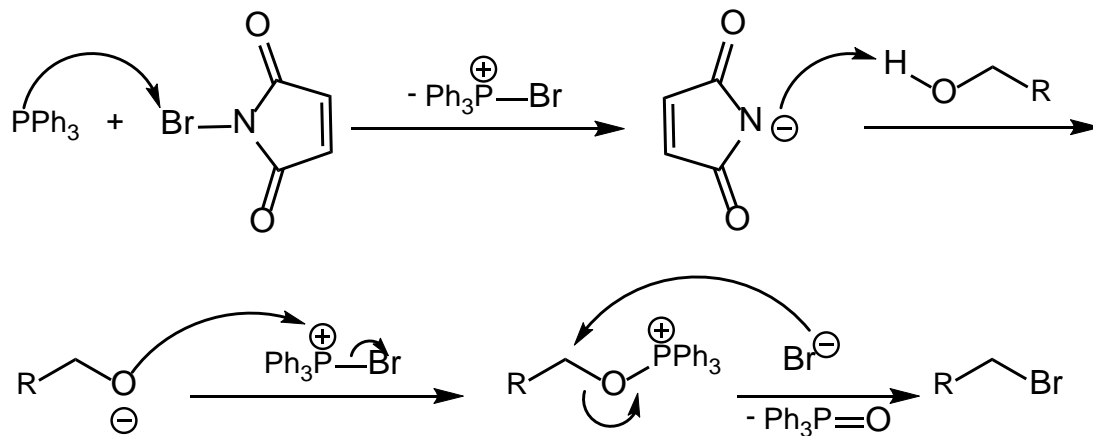
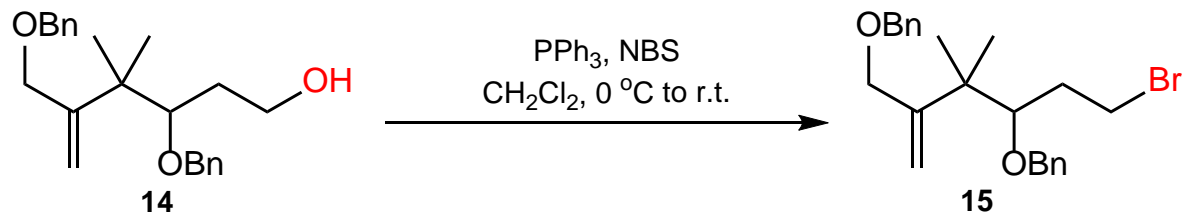
Total synthesis of Aplydactone



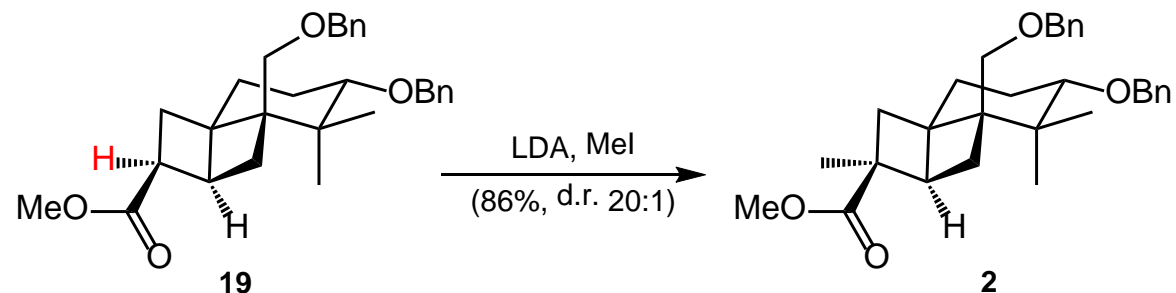
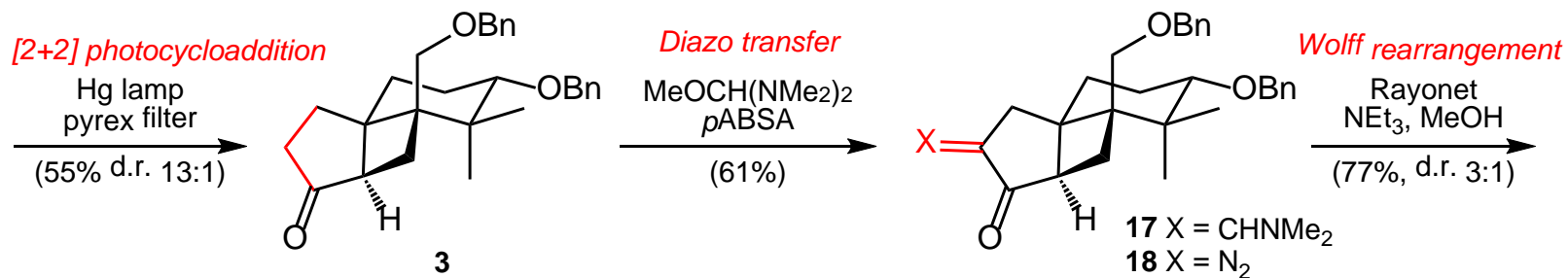
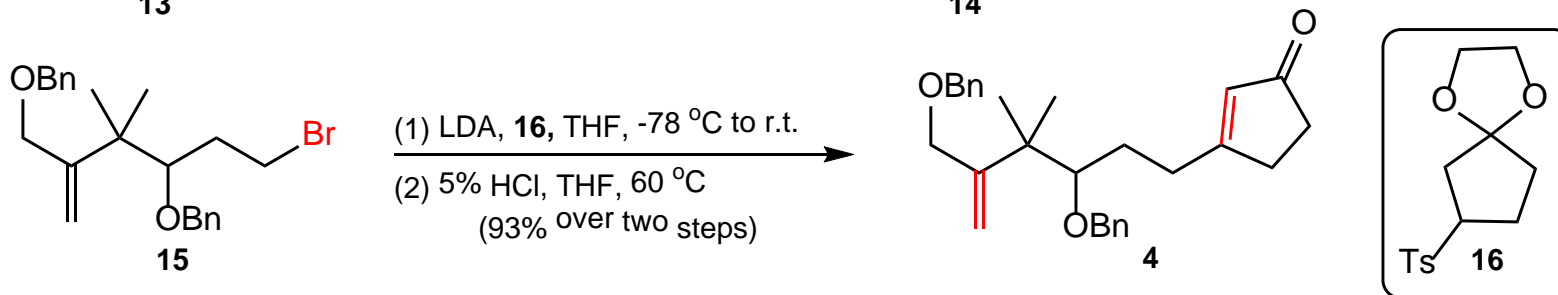
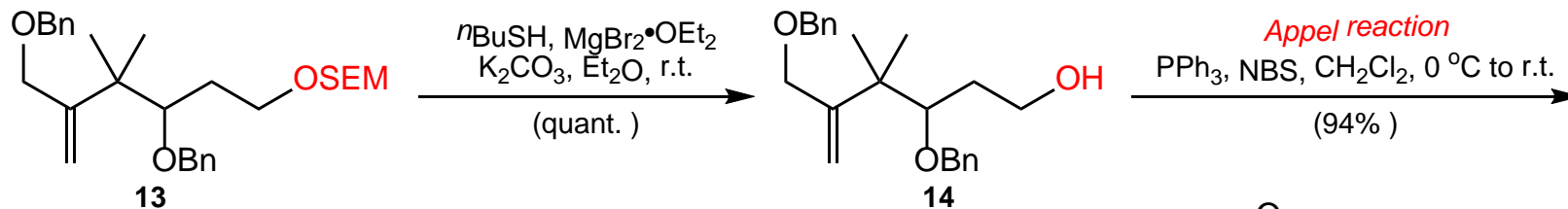
Total synthesis of Aplydactone



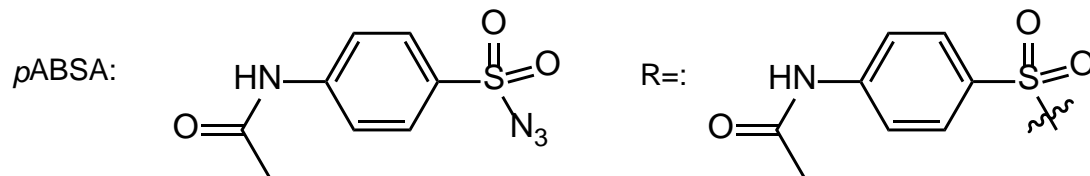
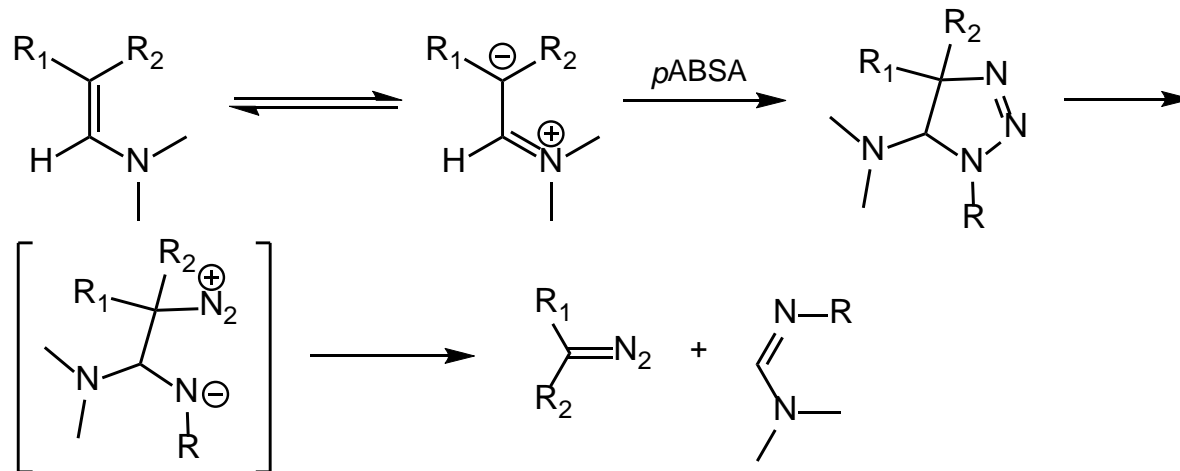
Appel reaction



Total synthesis of Aplydactone

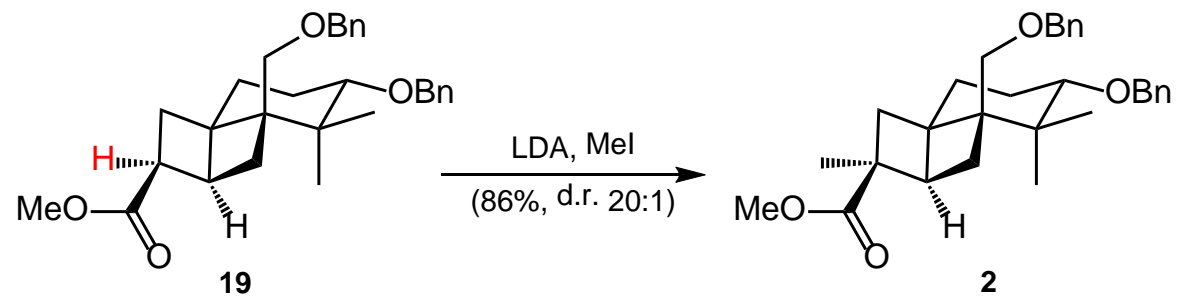
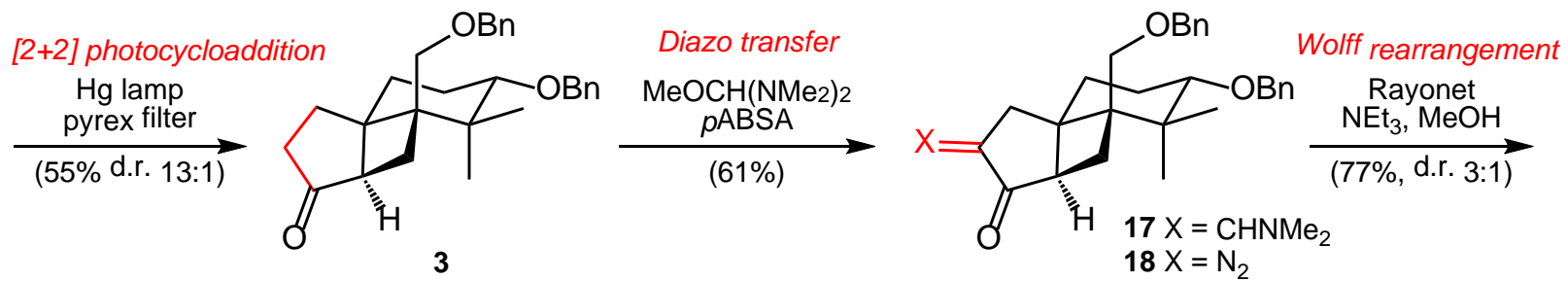
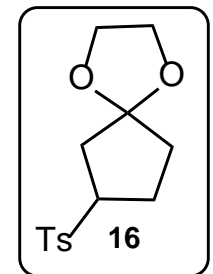
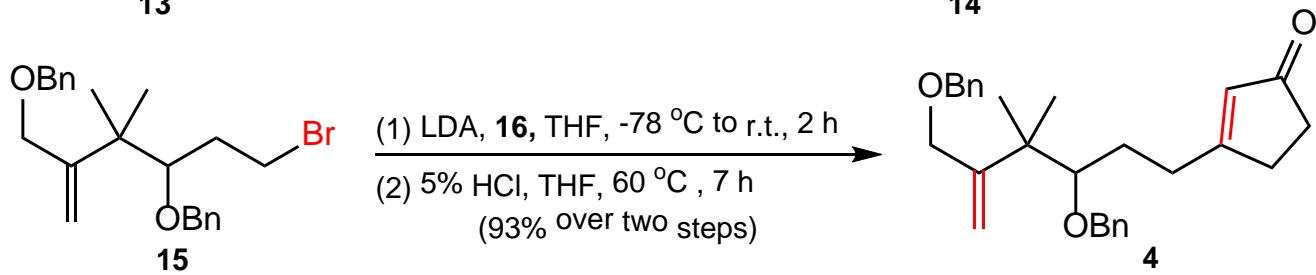
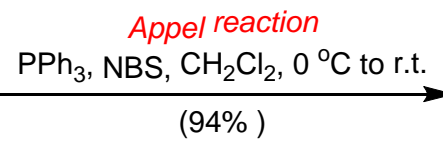
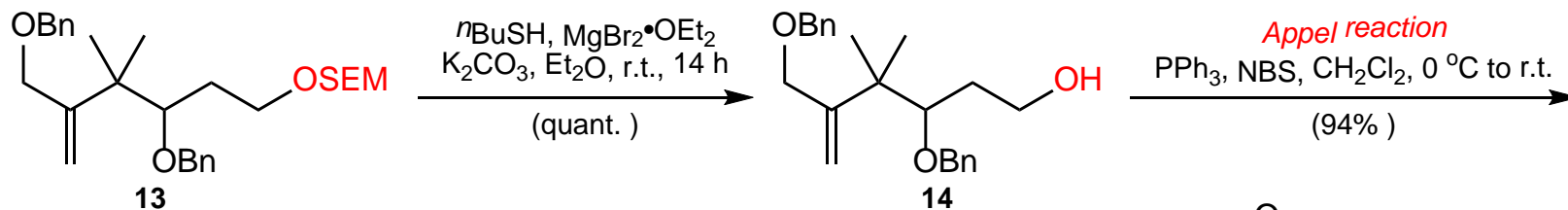


The formation of diazo ketone 18

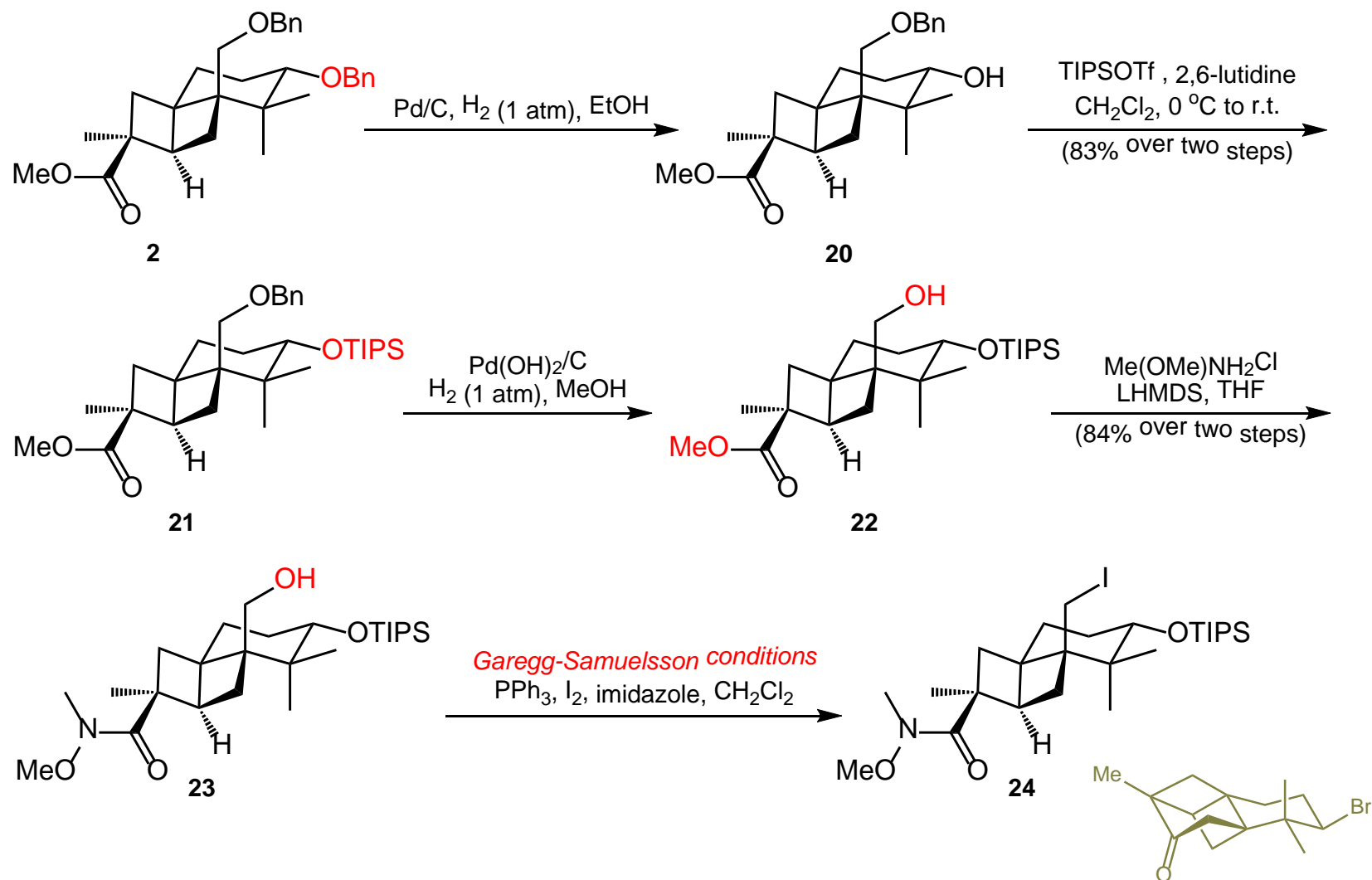


Himbert, G. *et al. Justus Liebigs Ann. Chem.* **1970**, 734, 70.

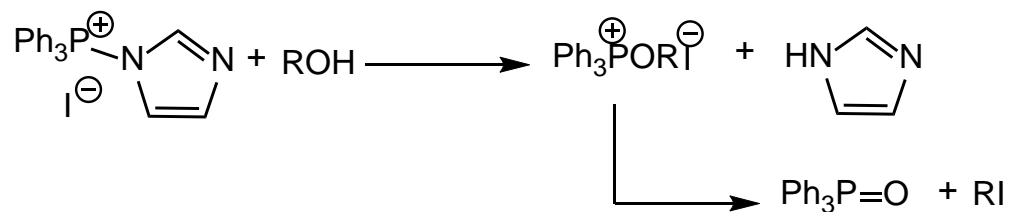
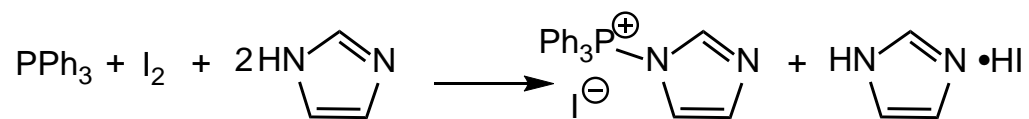
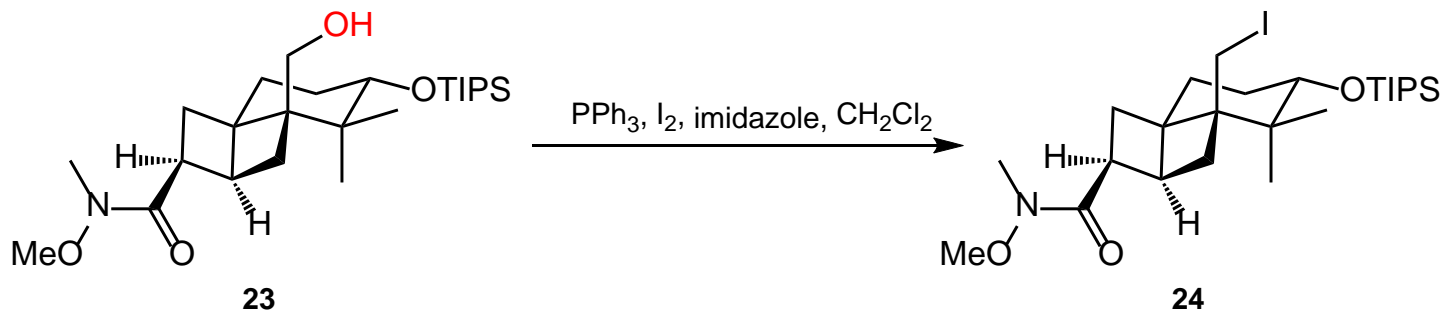
Total synthesis of Aplydactone



Total synthesis of Aplydactone

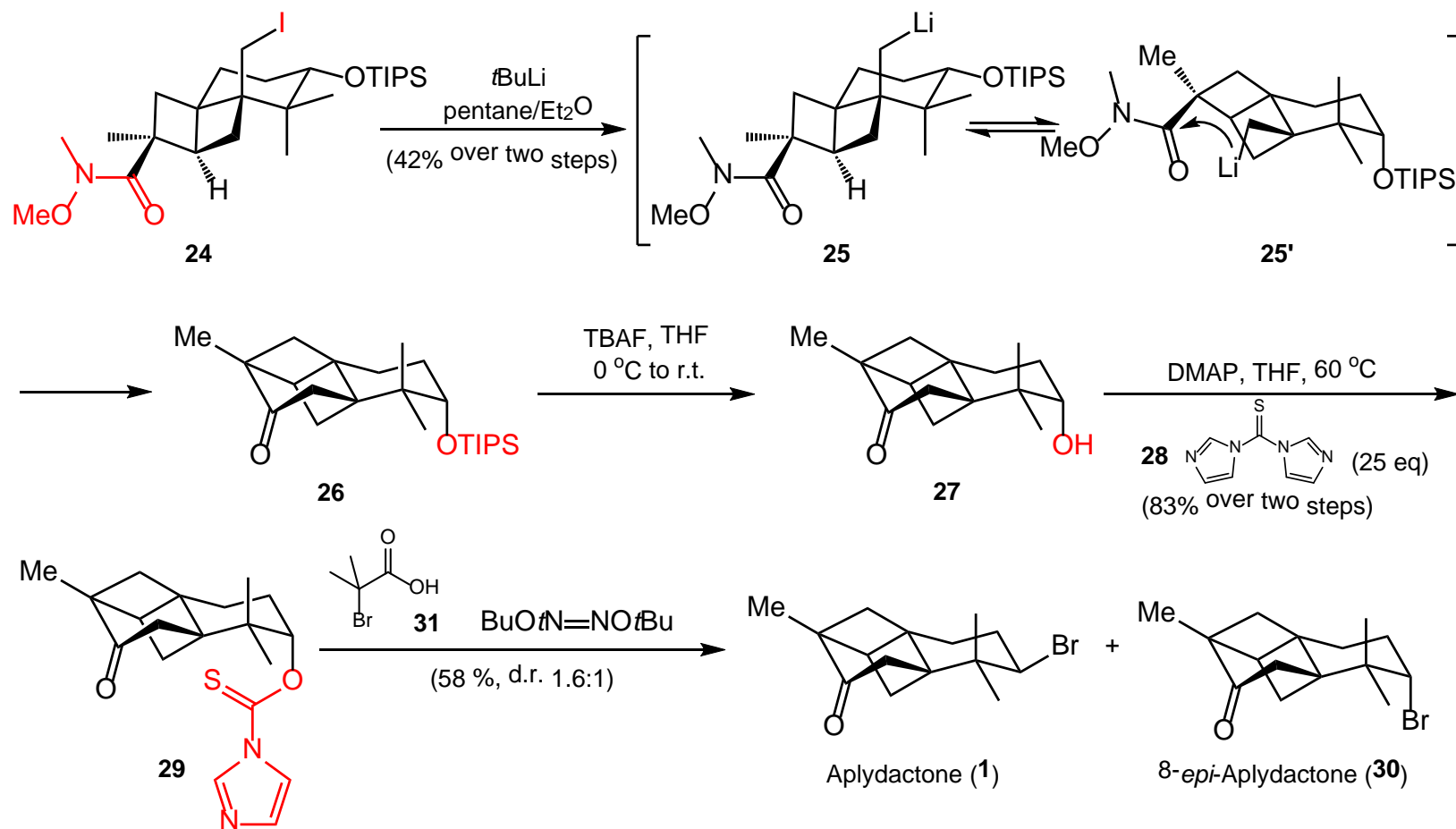


The formation of iodide 24

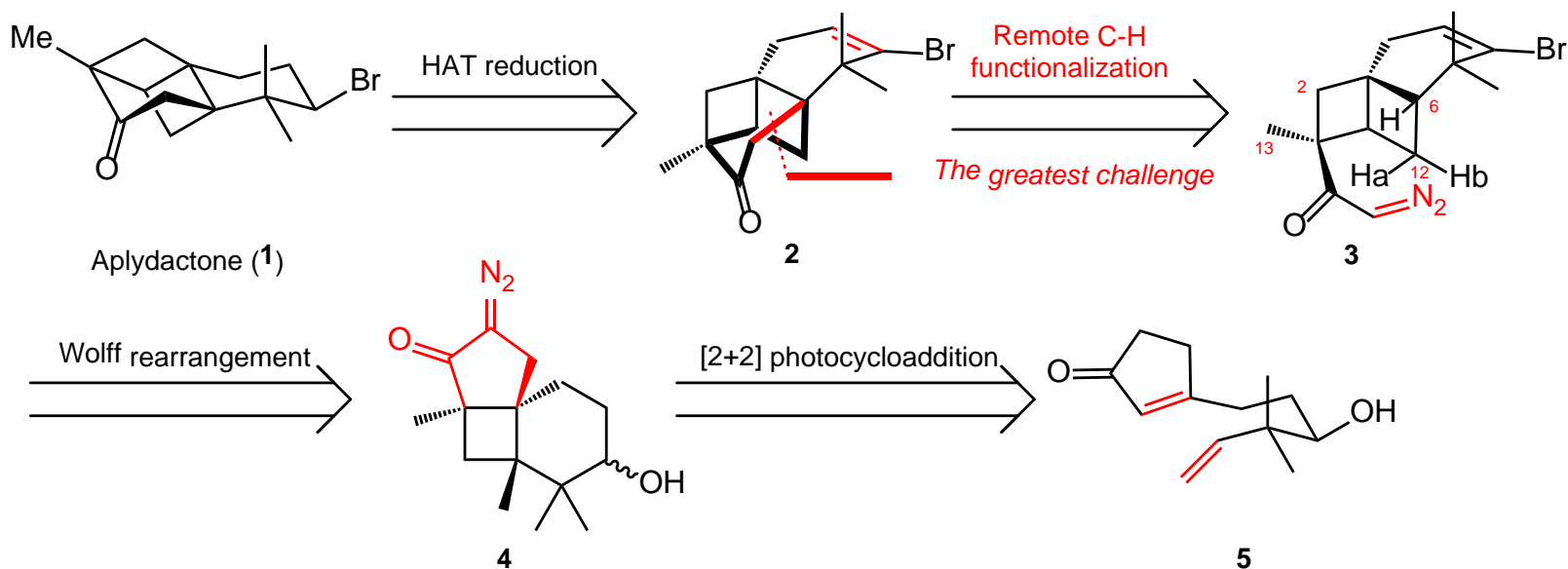


Poulter, C. D. *Tetrahedron Lett.* **1977**, 18, 1621.

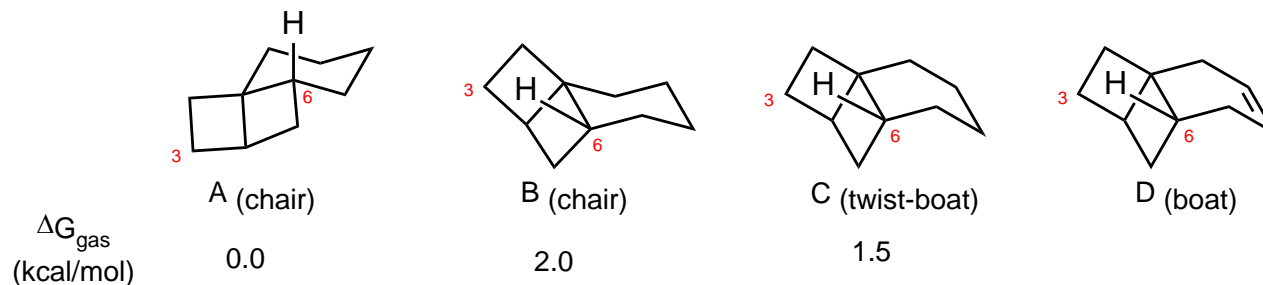
Total synthesis of Aplydactone



Retrosynthetic analysis of Aplydactone

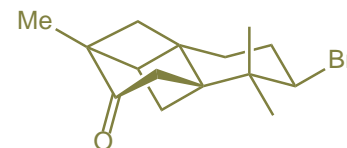
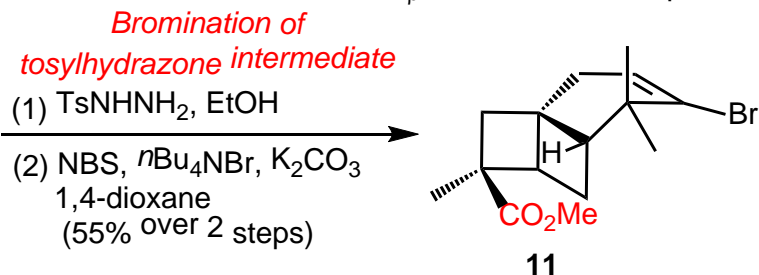
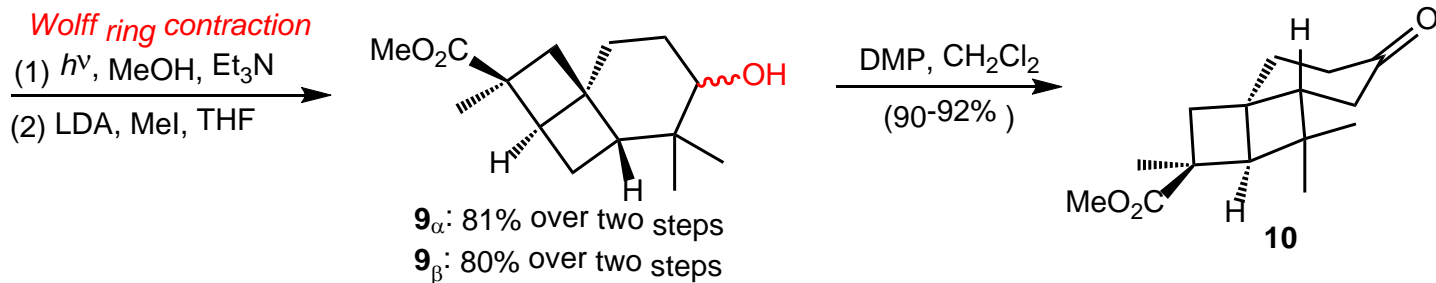
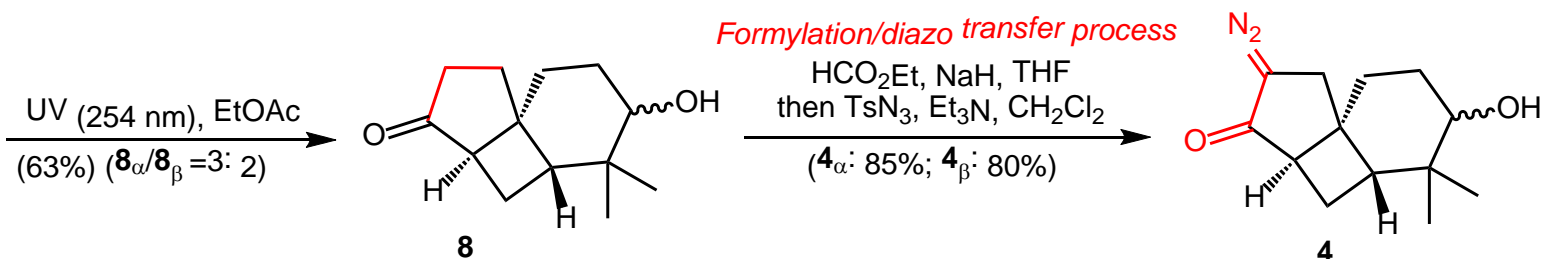
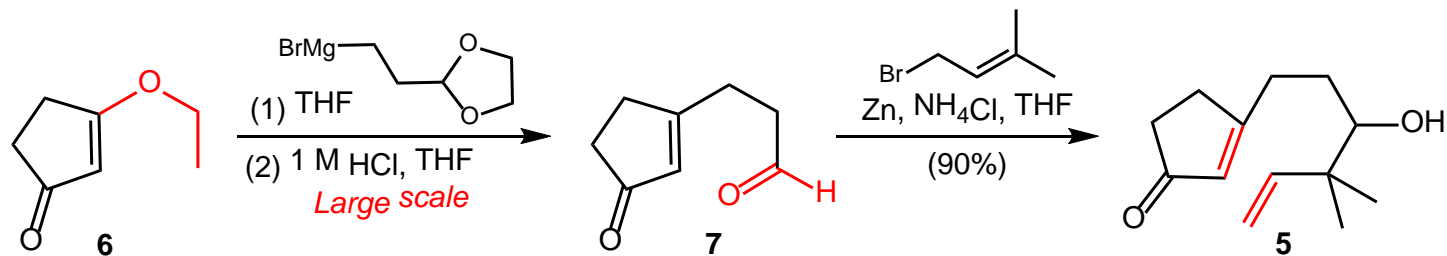


Conformational analysis of 6/4/4 tricycles

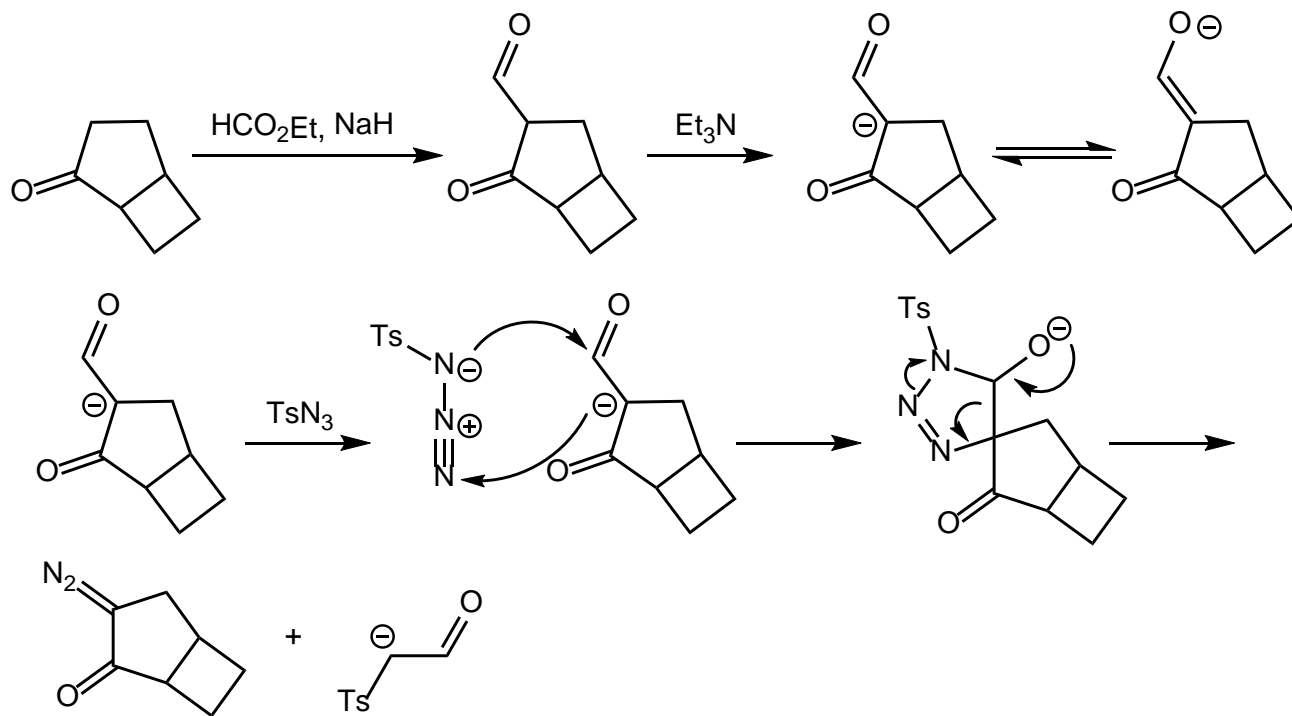
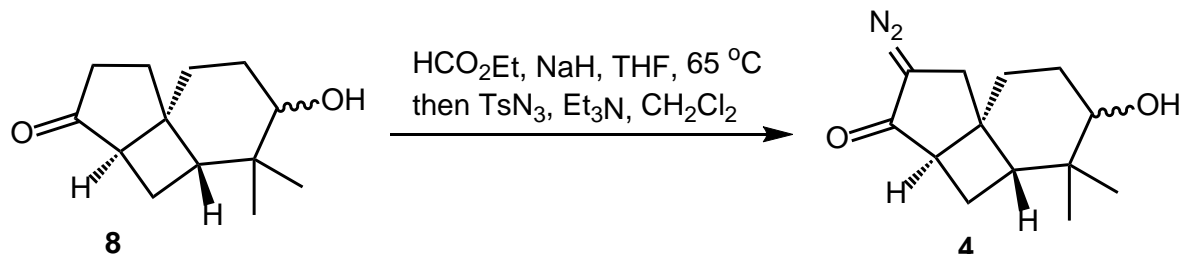


Zhang, Y.-D. *et al.* *Angew. Chem. Int. Ed.* **2017**, *56*, 8187.

Total synthesis of Aplydactone

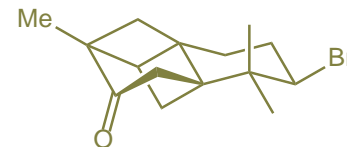
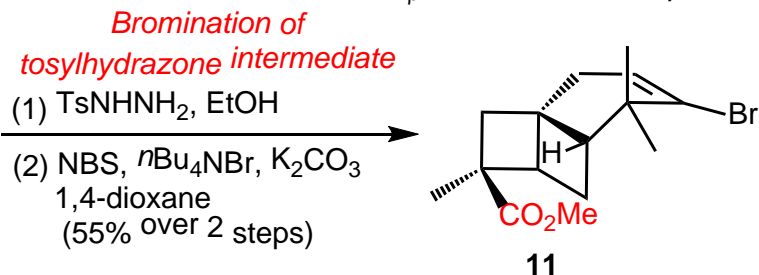
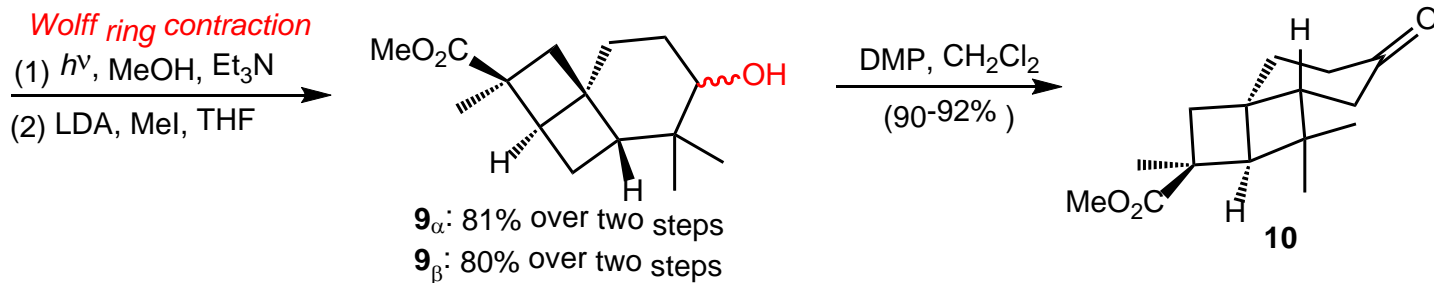
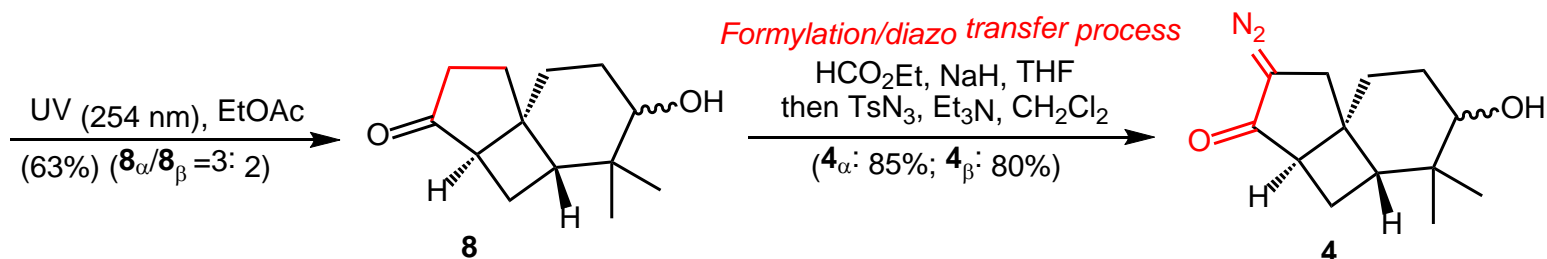
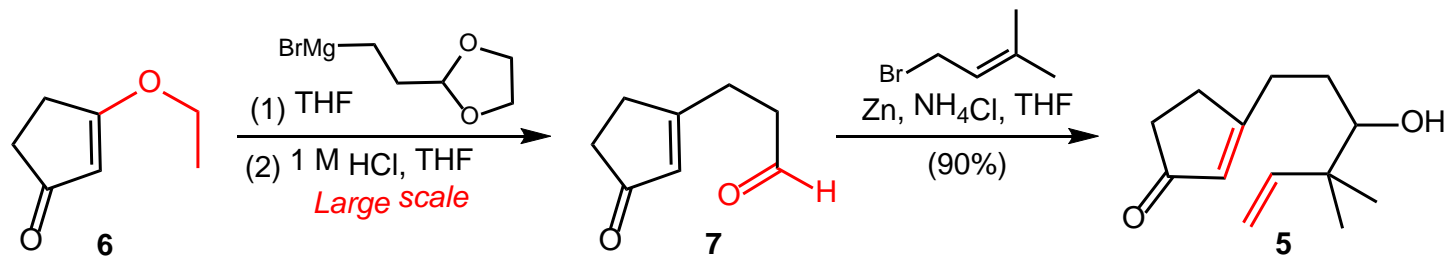


Formylation/diazo transfer process



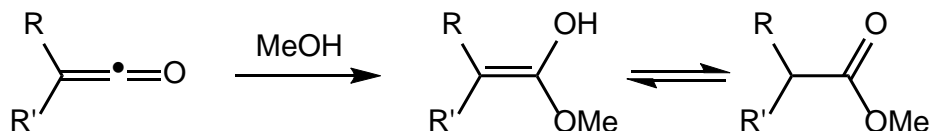
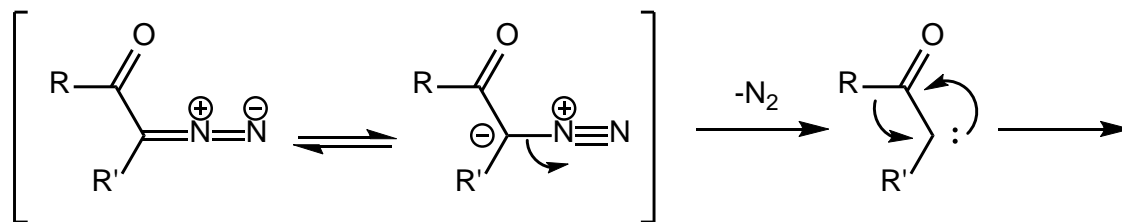
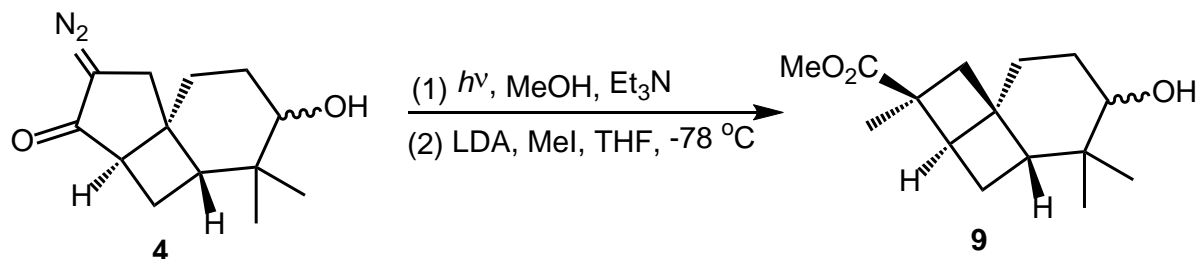
Menz, F. *et al. Chem. Ber.* **1968**, 101, 2622.

Total synthesis of Aplydactone

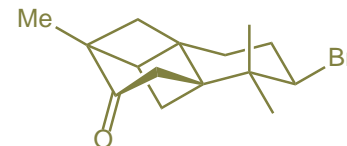
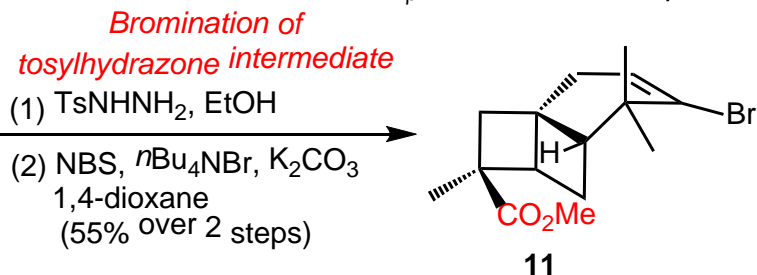
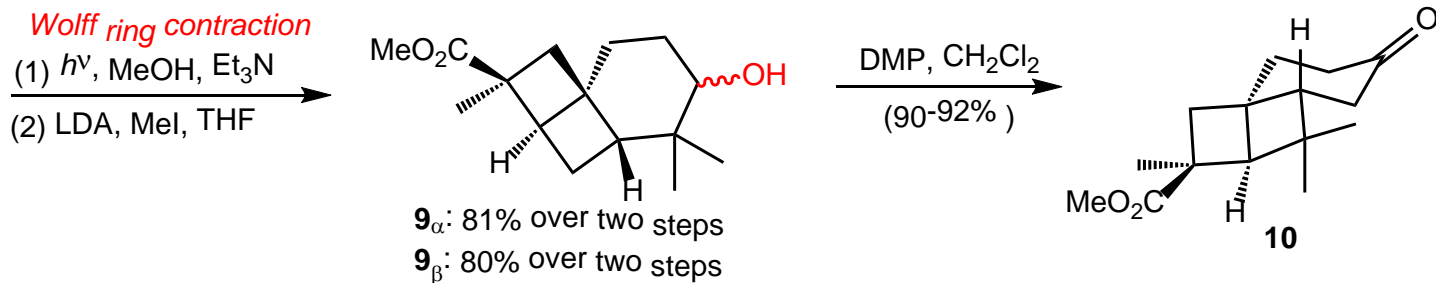
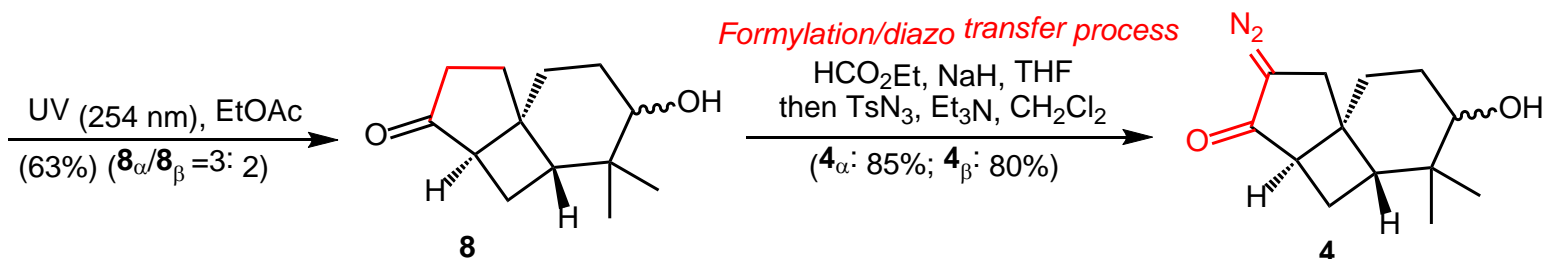
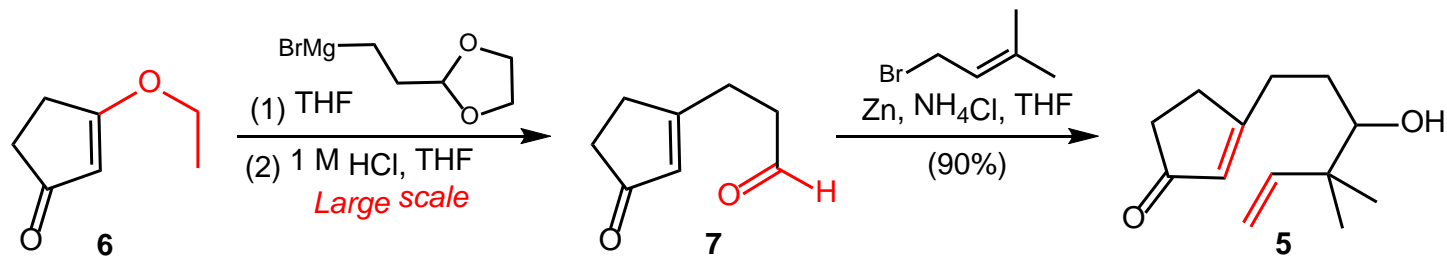


Wolff ring contraction

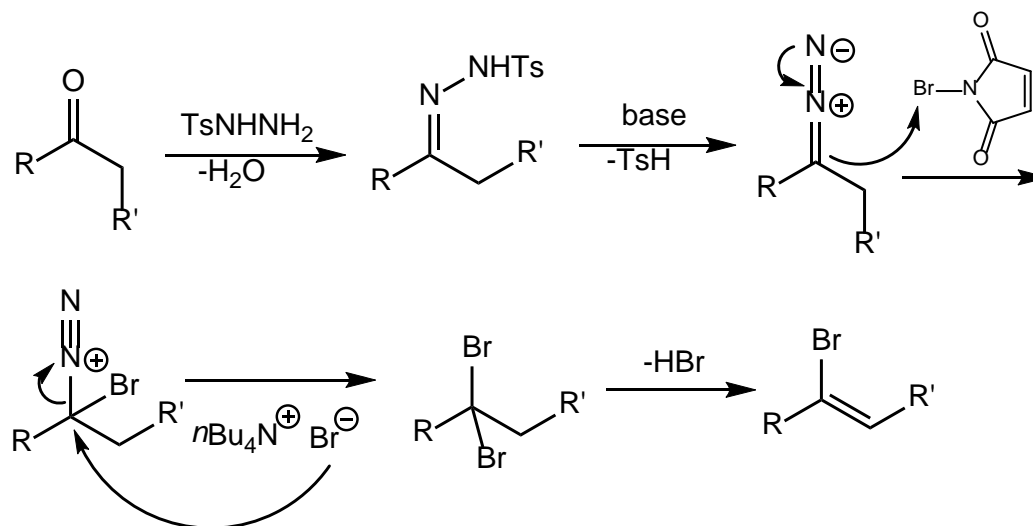
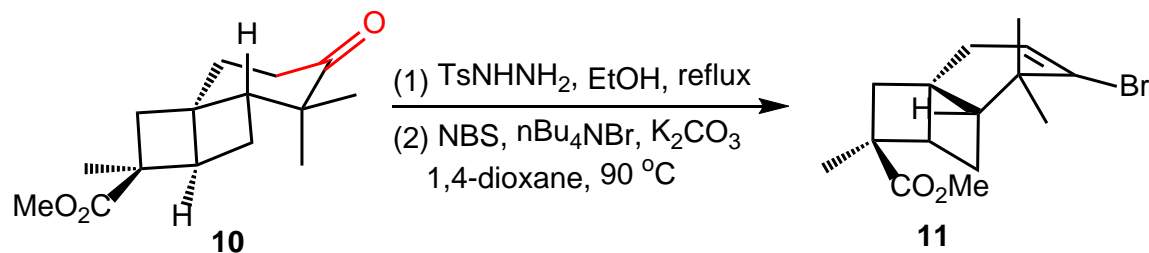
The Wolff Rearrangement allows the generation of ketenes from α -diazoketones. Wolff rearrangements that are conducted in the presence of nucleophiles generate derivatives of carboxylic acids



Total synthesis of Aplydactone

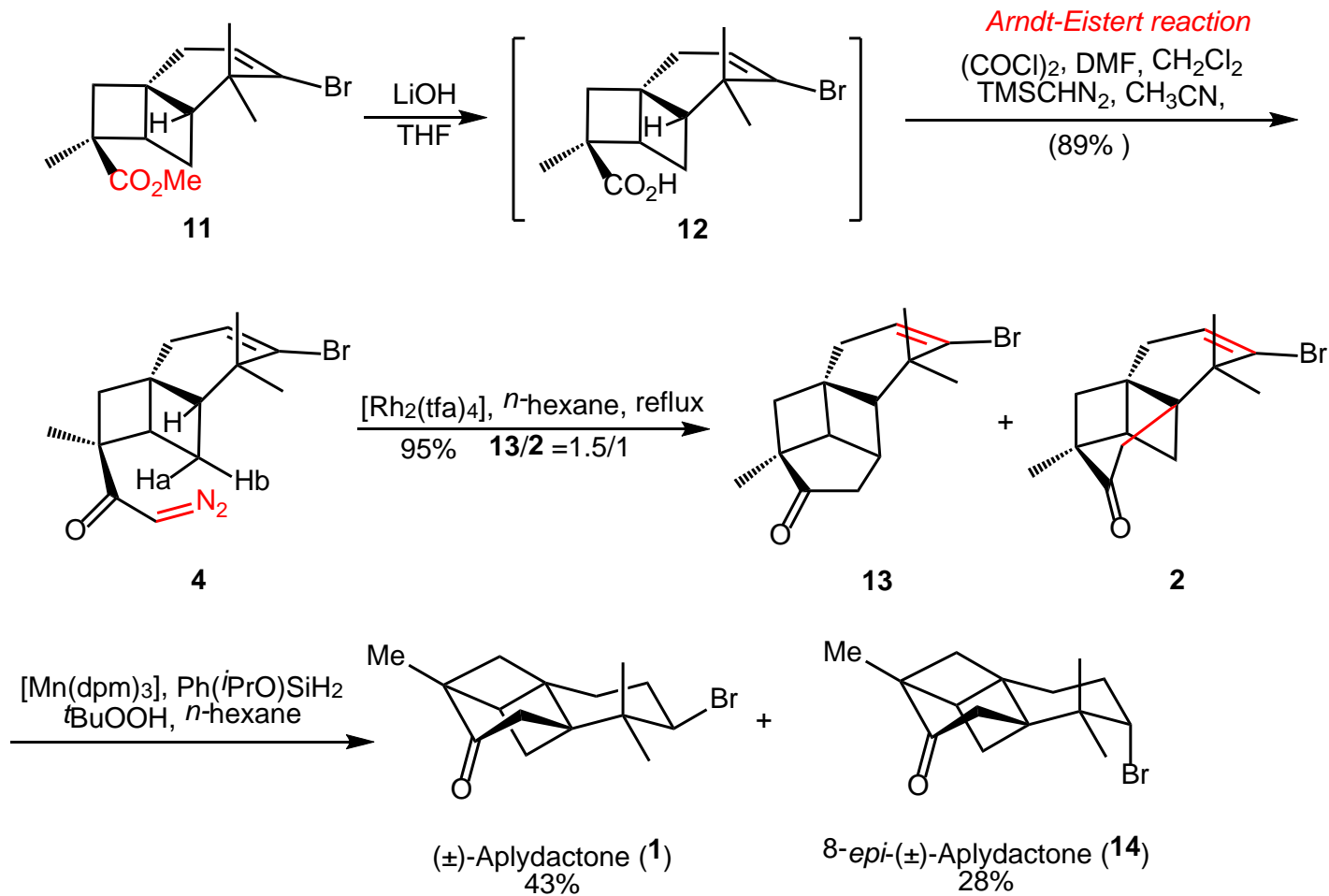


Bromination of a tosylhydrazone intermediate

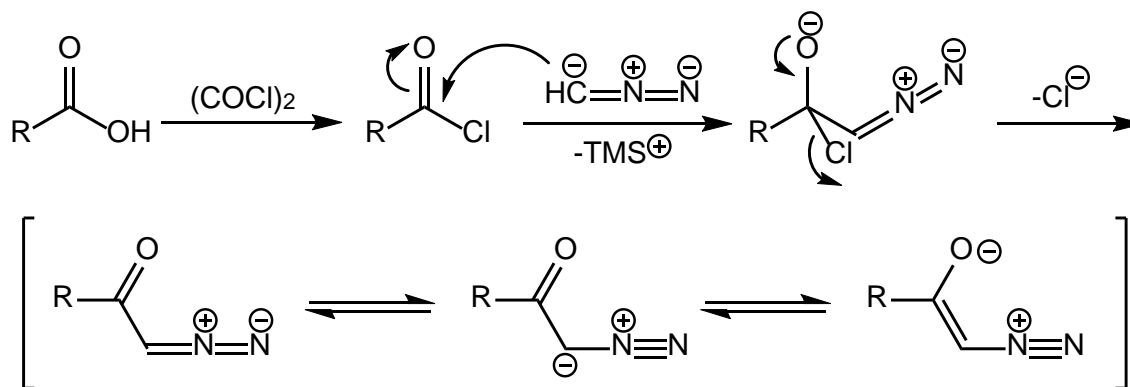
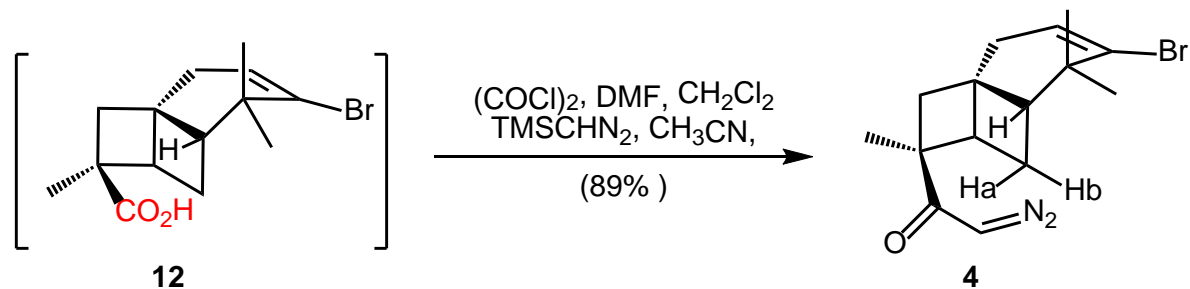


Prabhu, K. R. *et al.* *Org. Lett.* **2015**, *17*, 18.

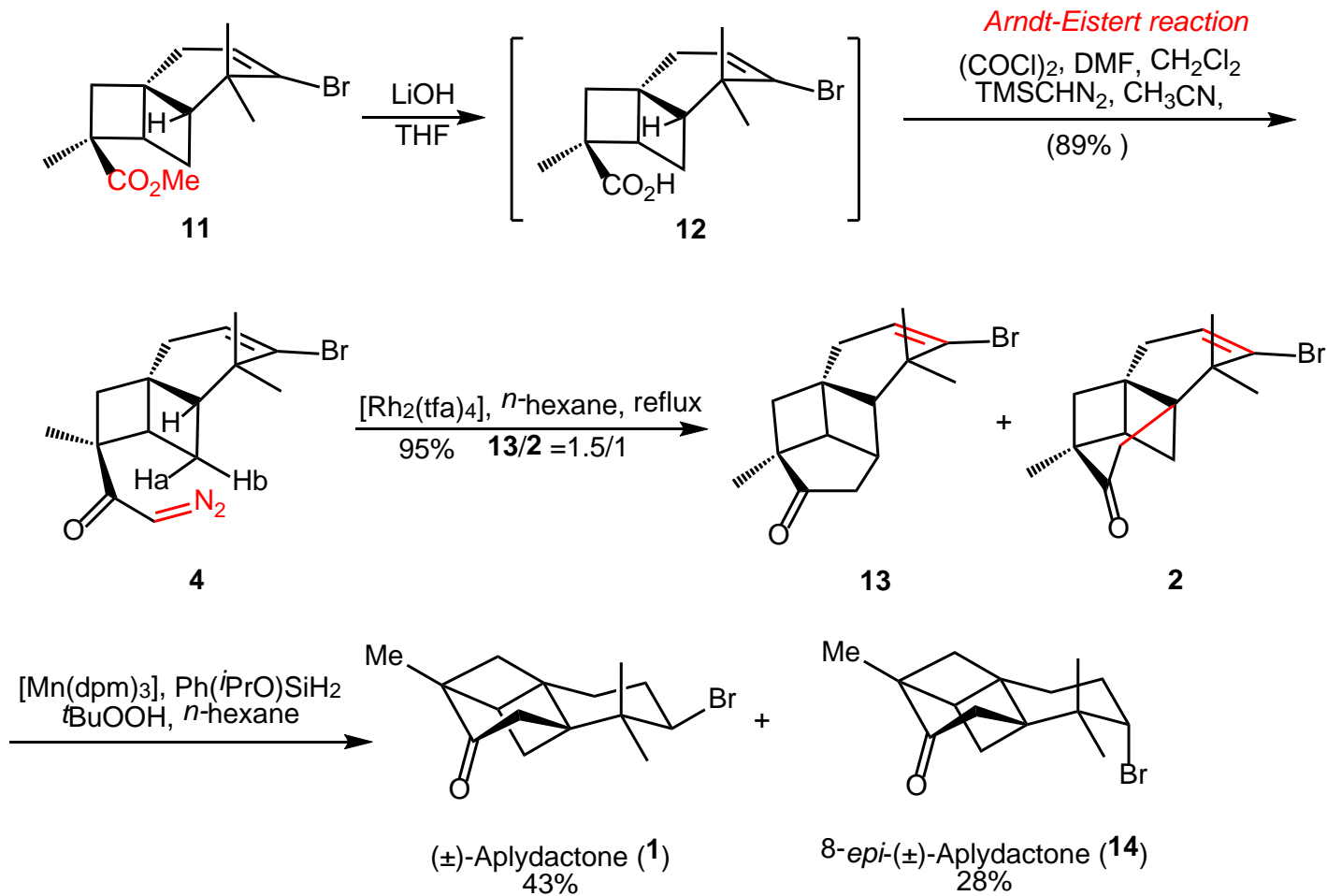
Total synthesis of Aplydactone



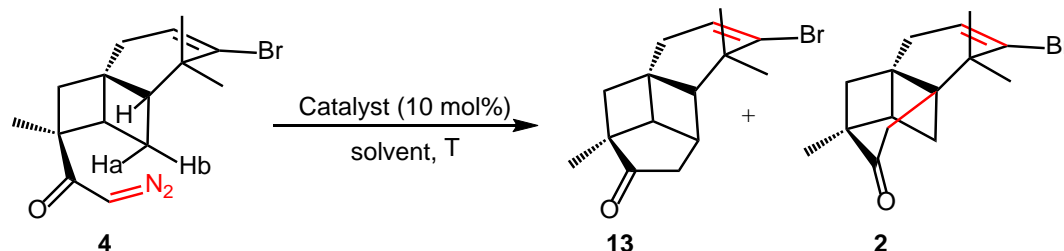
Arndt-Eistert reaction



Total synthesis of Aplydactone

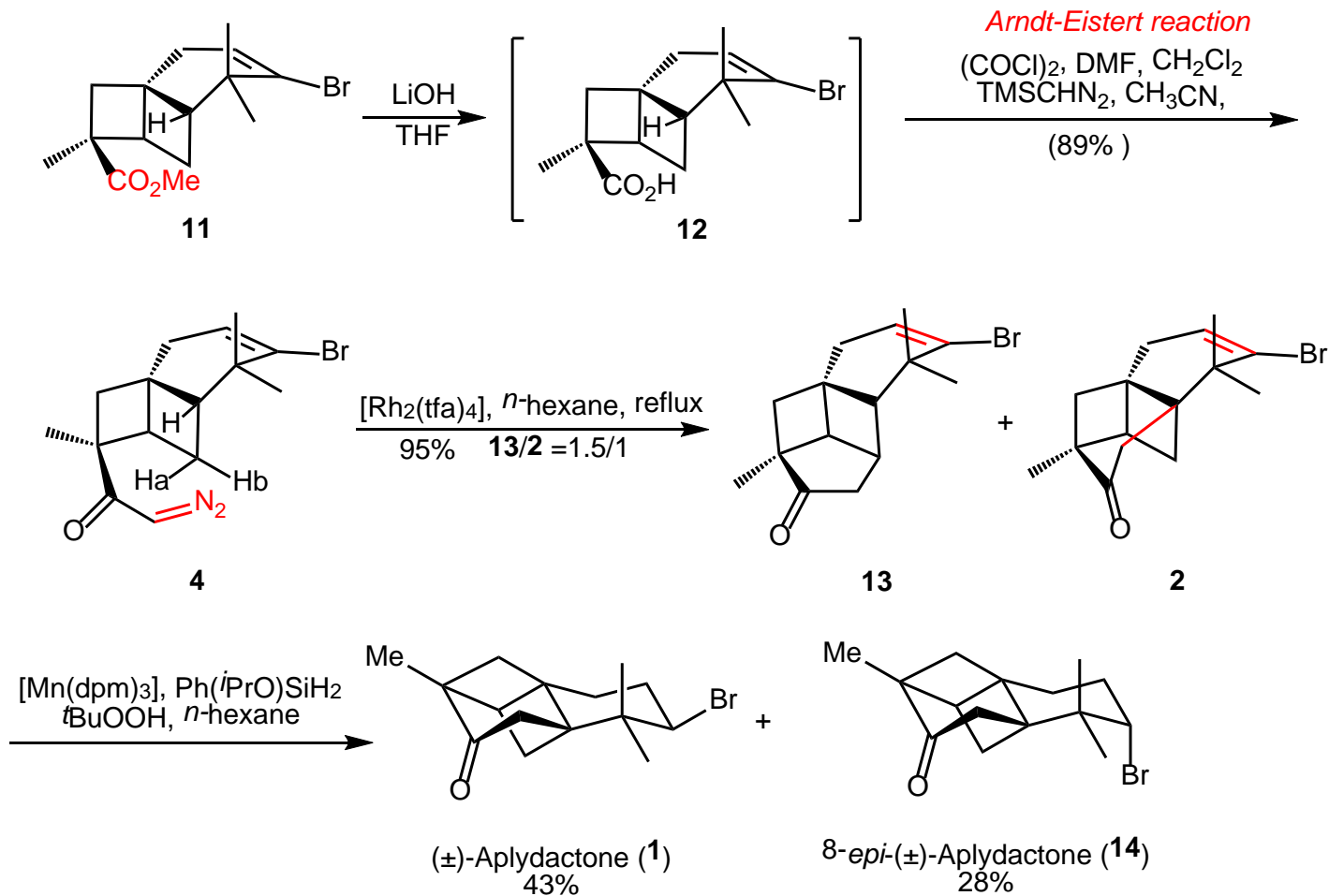


Optimization of reaction conditions of C-H insertion

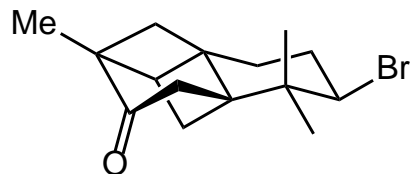


Entry	Catalyst	Solvent	T/°C	Yield/% (13/2)
1	[Rh ₂ (OAc) ₄]	DCM	RT	95 (4:1)
2	[Rh ₂ (cap) ₄]	DCM	RT	95 (27:1)
3	[Rh ₂ (esp) ₂]	DCM	RT	95 (2.4:1)
4	[Rh ₂ (pfb) ₄]	DCM	RT	95 (2.5:1)
5	[Rh ₂ (tfa) ₄]	DCM	RT	95 (2.2:1)
6	[Rh ₂ (tfa) ₄]	DCM	0	95 (2.2:1)
7	[Rh ₂ (tfa) ₄]	cyclohexane	RT	86 (1.7:1)
8	[Rh ₂ (tfa) ₄]	<i>n</i> -Hexane	RT	92 (1.7:1)
9	[Rh ₂ (tfa) ₄]	<i>n</i> -Hexane	69	95 (1.5:1)

Total synthesis of Aplydactone



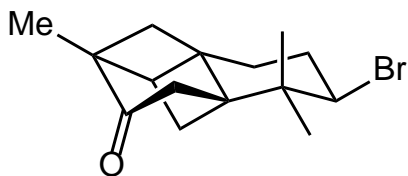
Summary



Aplydactone

- 24 Steps, 0.56% overall yield;
- The first total synthesis of aplydactone;
- Diastereoselective [2+2] cycloaddition;
- Photochemical Wolff rearrangement.

Trauner, D. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 11251.



Aplydactone

- 12 Steps, 4.5% overall yield;
- A finely tuned conformation, supported by theoretical calculations;
- Remote C-H functionalization strategy;
- Protecting-group-free;
- HAT reaction.

Zhang, Y.-D. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 8187.

The first paragraph

Aplydactone is a halogenated terpene natural product from the sea hare *Aplysia dactylomela* and was first disclosed by Stonik and co-workers in 2001. Structurally, aplydactone features a highly strained tetracyclic framework consisting of two six-membered rings and a [2]-ladderane system (two fused four-membered rings). Notably, the tetracycle also comprises four quaternary centers and three of them reside on the ring junctions of the four-membered rings, which are prone to a Wagner–Meerwein rearrangement induced by an adjacent carbon cation species. Although Stonik et al. assumed that aplydactone biosynthetically derived from the chamigrane sesquiterpene dactylone through an intramolecular [2+2] photocycloaddition, their preliminary attempts at this conversion failed.

The first paragraph

Collectively, the structural features, as well as uncertain biosynthetic hypothesis, make aplydactone an intriguing but challenging target for chemical synthesis.

The last paragraph

In summary, we have achieved a concise total synthesis of highly strained marine sesquiterpene aplydactone through a remote C-H functionalization strategy. Our approach relies on a transannular C-H insertion to close the cyclohexanone ring over the [2]-ladderane scaffold and HAT reaction to install the bromine-containing stereocenter. A finely tuned conformation, supported by theoretical calculations, is the key for the success of the challenging C-H insertion. To our knowledge, this is the first time that a transannular sixmembered ring C-H insertion has been successfully applied to a complex molecule synthesis. While the yield for this application is only moderate, this method enabled a protecting-group-free approach to aplydactone with decent overall efficiency.

The last paragraph

Our synthesis also demonstrates that nontraditional disconnections based on C-H functionalization in synthesis planning can not only positively influence complex molecule assembly, but also promote the discovery of otherwise difficult-to-make analogues of natural product.

Acknowledgement

***Thanks
for your attention***