Literature Report I

Total Synthesis of Hamigerans

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Checker: Shu-Bo Hu
Date: 2016-11-28

Li, X.; Xue, D.; Wang, C.; Gao, S.
Angew. Chem. Int. Ed. **2016**, *55*, 9942.

CV of Shuanhu Gao

Education:

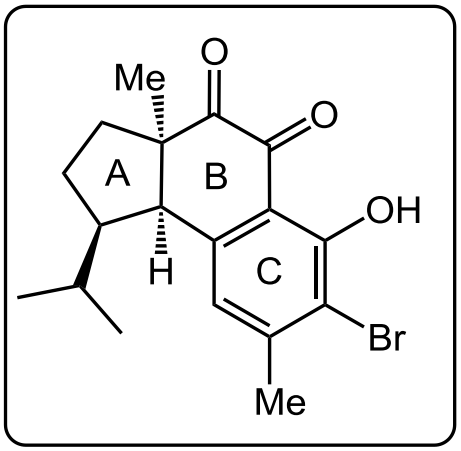
- **1997–2001** B.S., Lanzhou University
- **2001–2006** Ph.D., Lanzhou University
- **2006–2010** Postdoc., UT Southwestern Medical Center
- **2010–2016** Professor, East China Normal University

Research:

➢ Using modern synthetic chemistry to address biologically structurely novel natural target molecules, such as naturally occurring alkaloids, polyketides and terpenoids.

Contents

Introduction



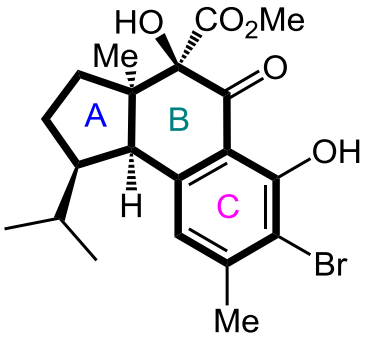
Hamigeran B

Sponge

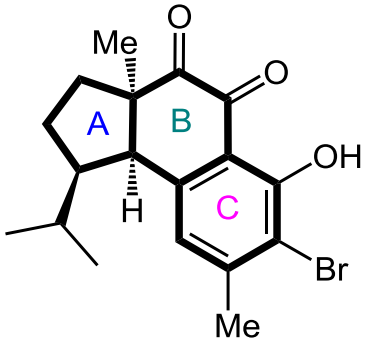
- Isolated from *poecilosclerid sponge* in 2000;
- Exhibiting promising *anti*-herpes and poliovirus activity;
- Three stereocenters, A-B-C rings and polysubstituted aromatic ring.

Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod*. **2000**, *63*, 79.

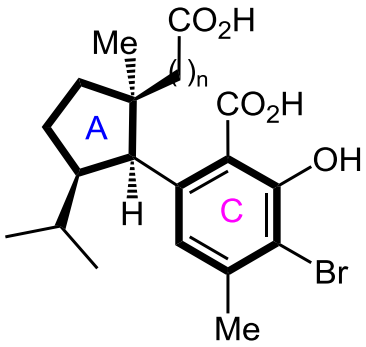
Introduction



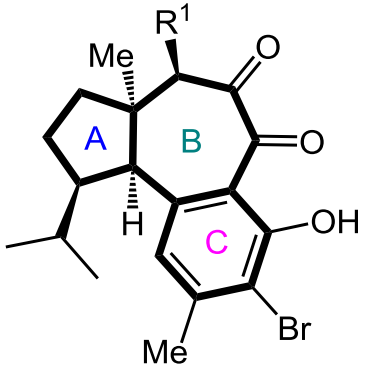
Hamigeran A (**1**)
5-6-6 [A-B-C]



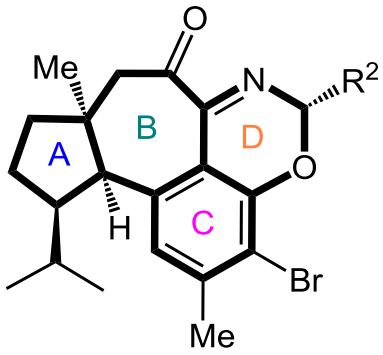
Hamigeran B (**2**)
5-6-6 [A-B-C]



n = 0, Hamigeran E (**3**)
n = 1, Hamigeran L (**4**)
5-6 [A-C]



R^1 = OAc, Hamigeran C (**5**)
R^1 = H, Hamigeran G (**6**)
5-7-6 [A-B-C]



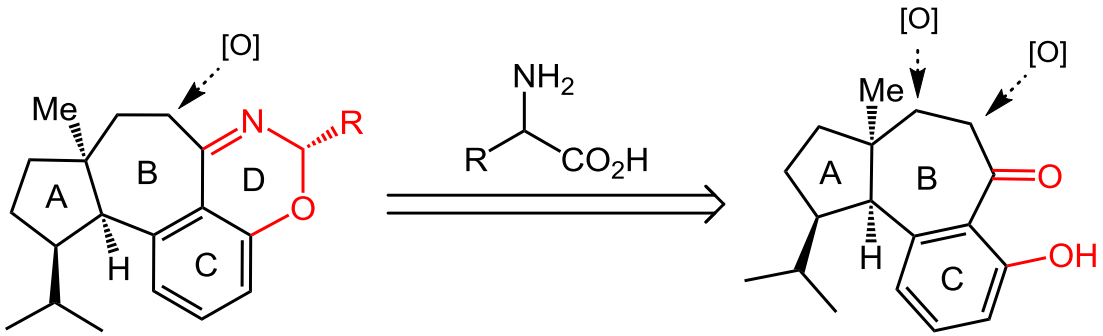
5-7-6-6 [A-B-C-D]

R^2 = Me, Hamigeran D (**7**)
R^2 = Bn, Hamigeran N (**8**)
R^2 = *i*Pr, Hamigeran O (**9**)
R^2 = *i*Bu, Hamigeran P (**10**)
R^2 = *s*Bu, Hamigeran Q (**11**)

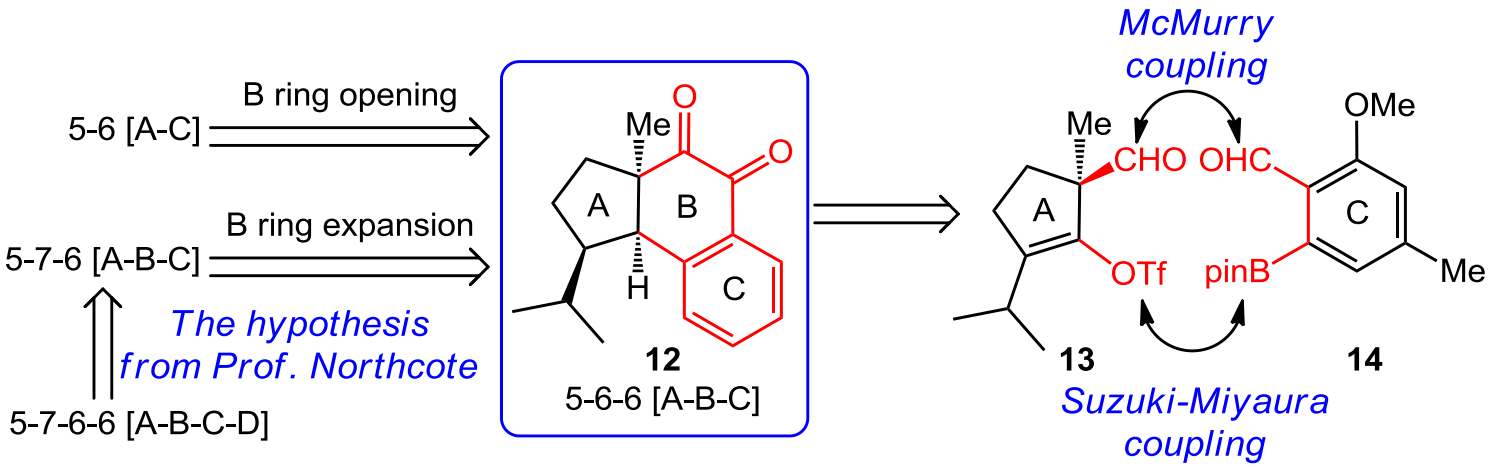
Northcote, P. T.; Dattelbaum, J. D.; Singh, A. J.; Field, J. J.; Miller, J. H. *J. Org. Chem*. **2015**, *80*, 304.

Retrosynthetic analysis

The hypothesis from Prof. Northcote:

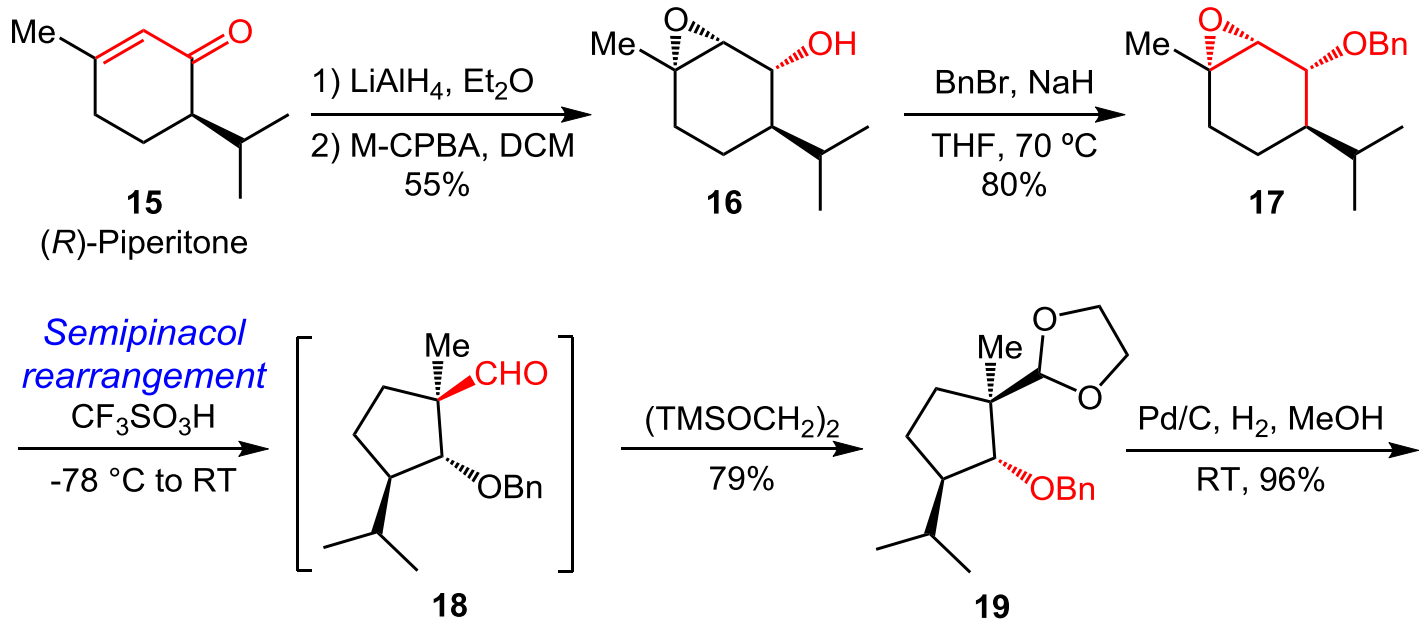


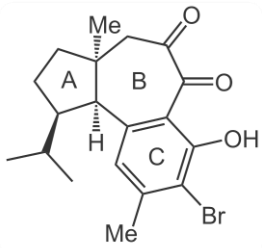
5-7-6-6 [A-B-C-D] 5-7-6 [A-B-C]



Northcote, P. T.; Dattelbaum, J. D.; Singh, A. J.; Field, J. J.; Miller, J. H. *J. Org. Chem*. **2015**, *80*, 304.

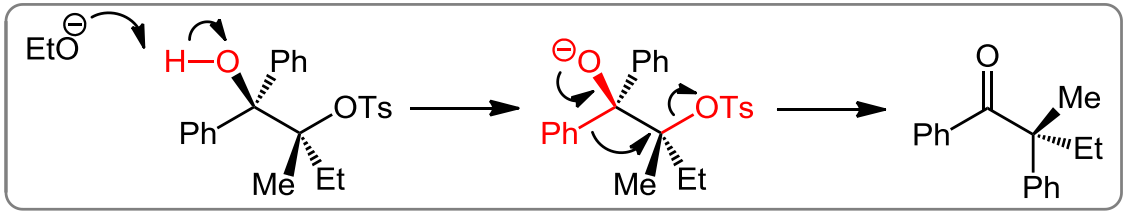
The synthesis of 13





Semipinacol rearrangement

Type 1



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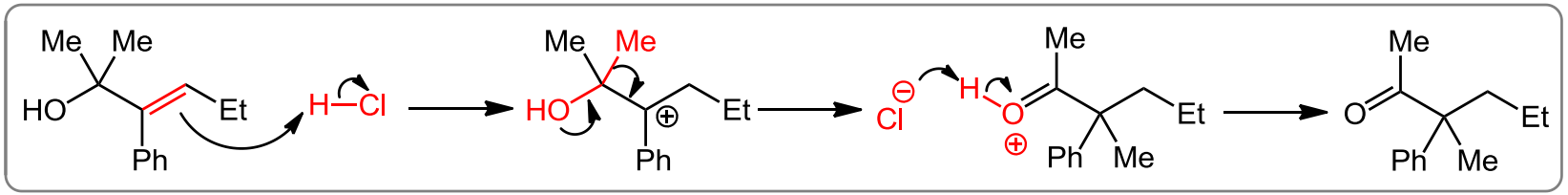

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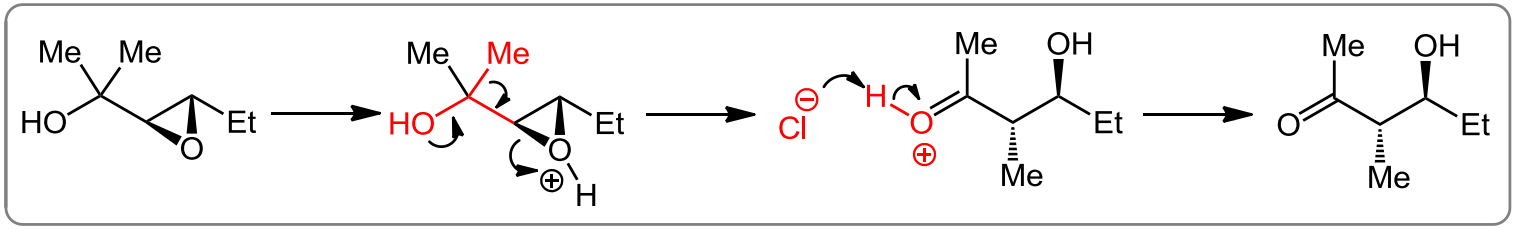
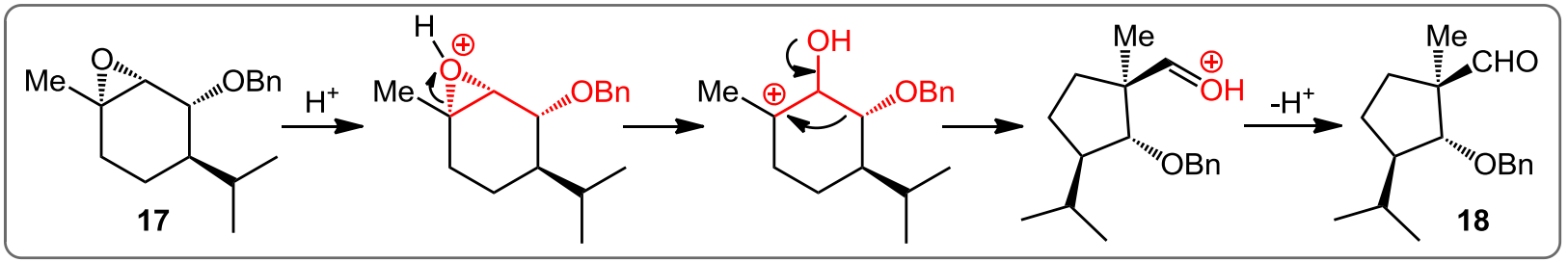
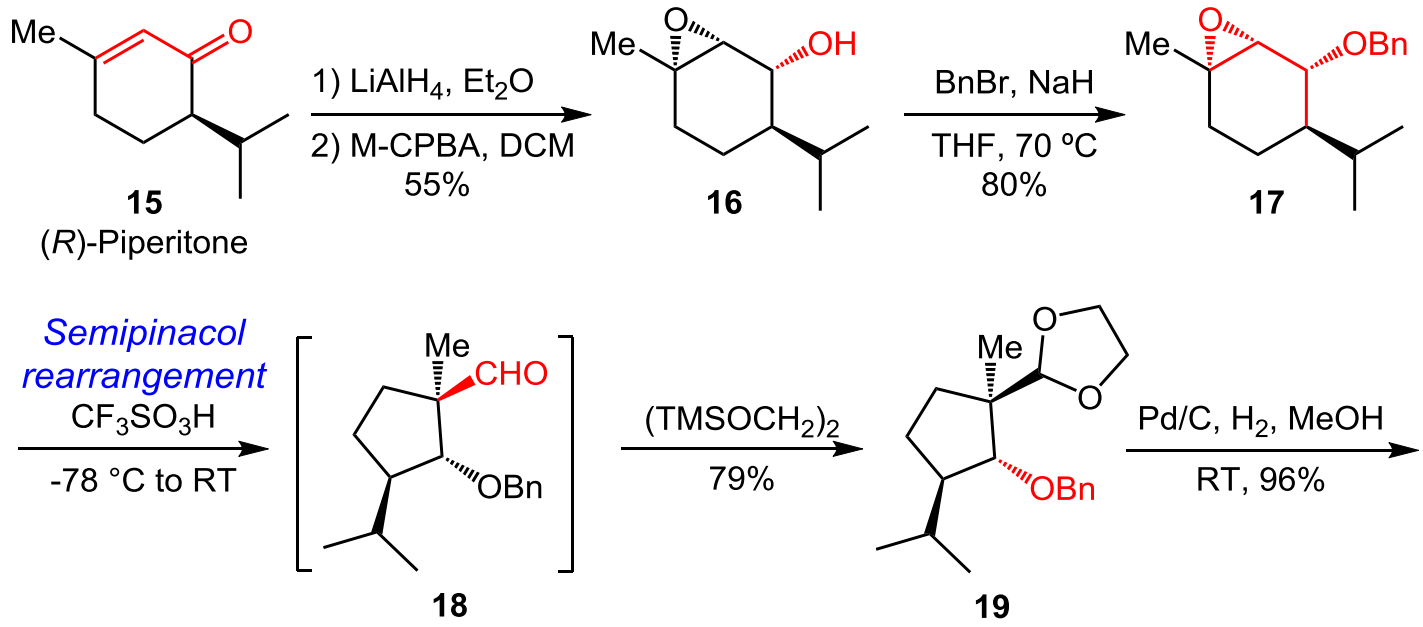
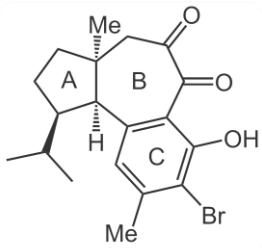


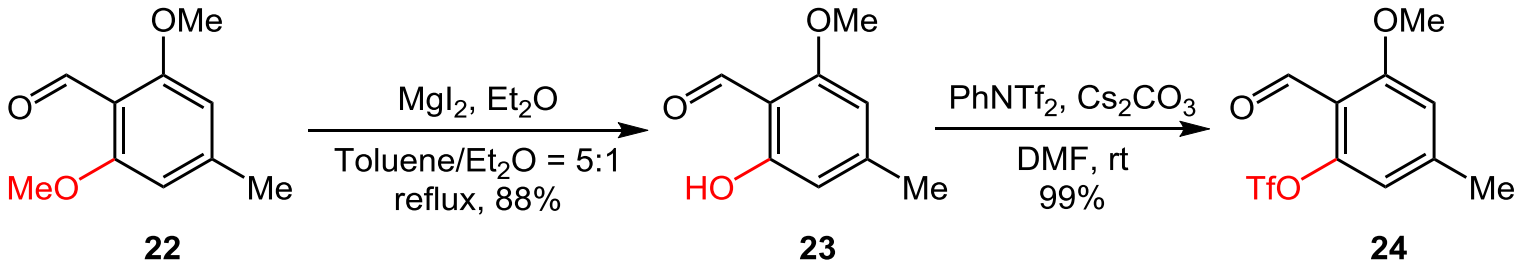


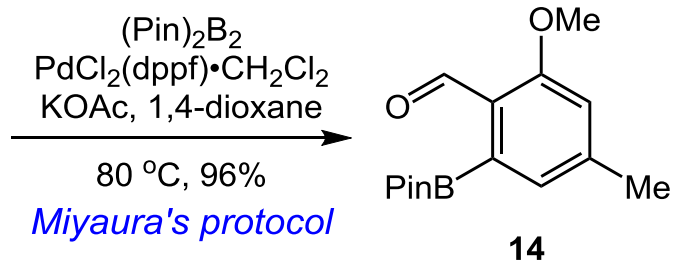
The synthesis of 13

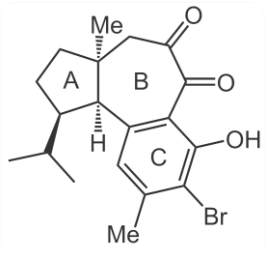


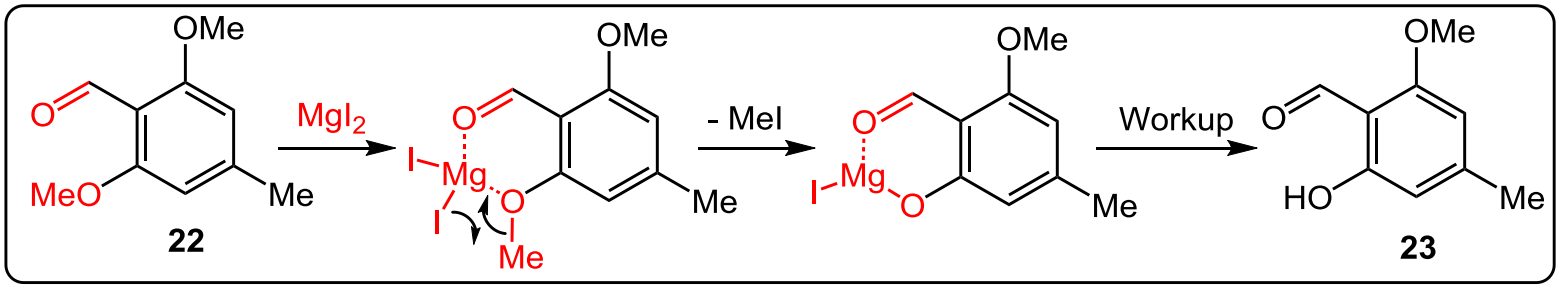


The synthesis of 14

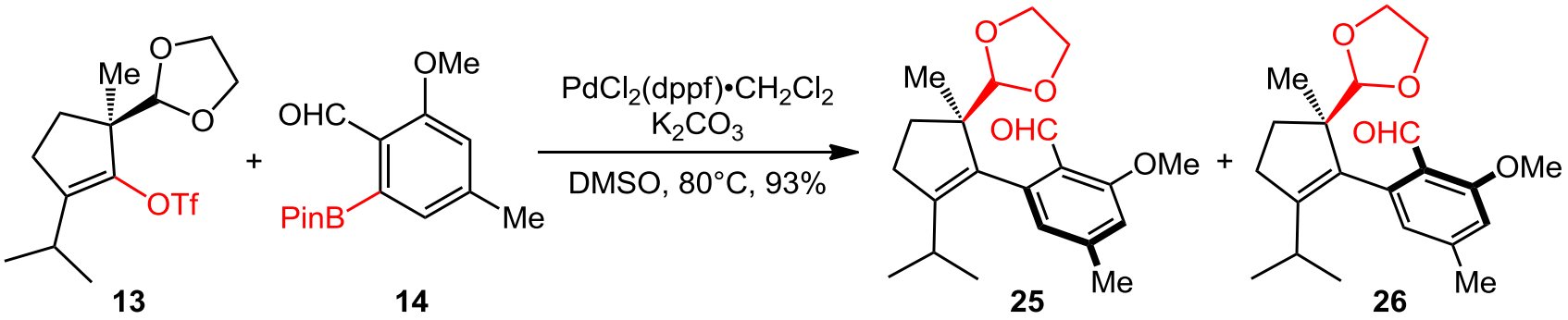


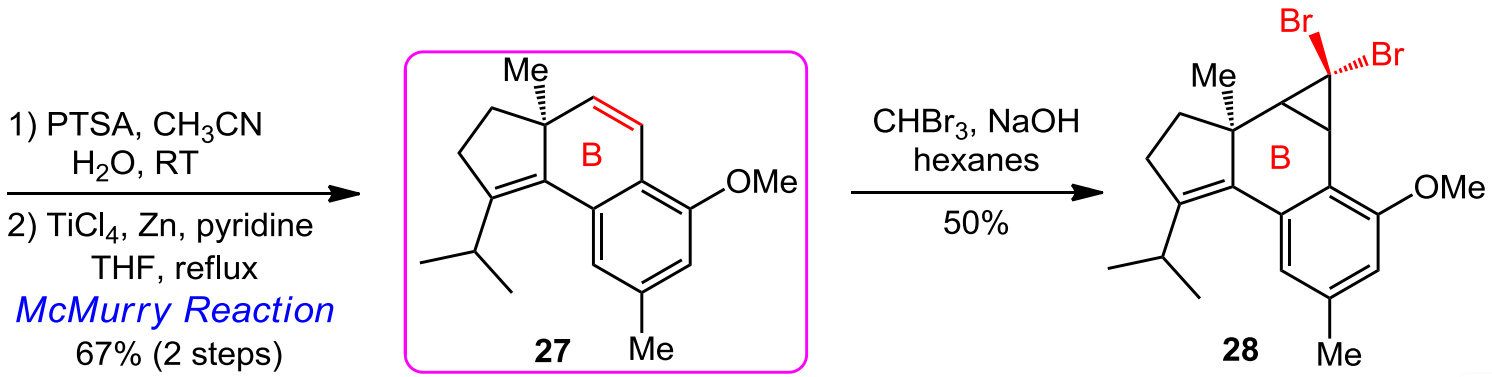


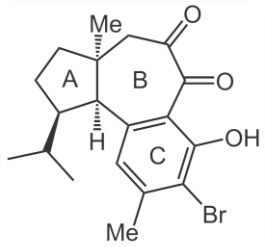




Attempt at the B ring expansion

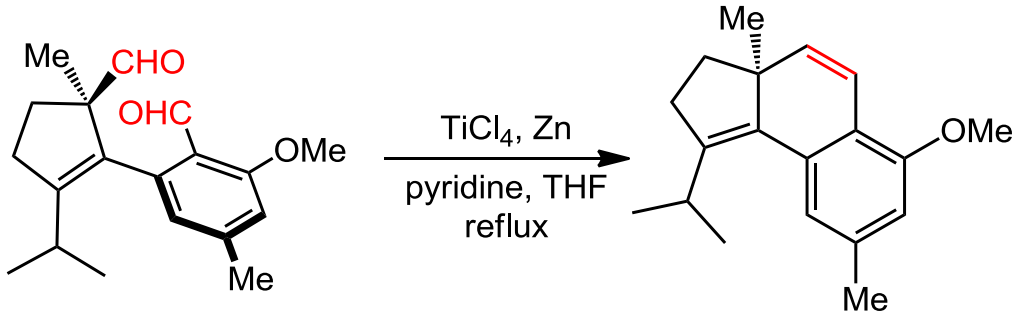


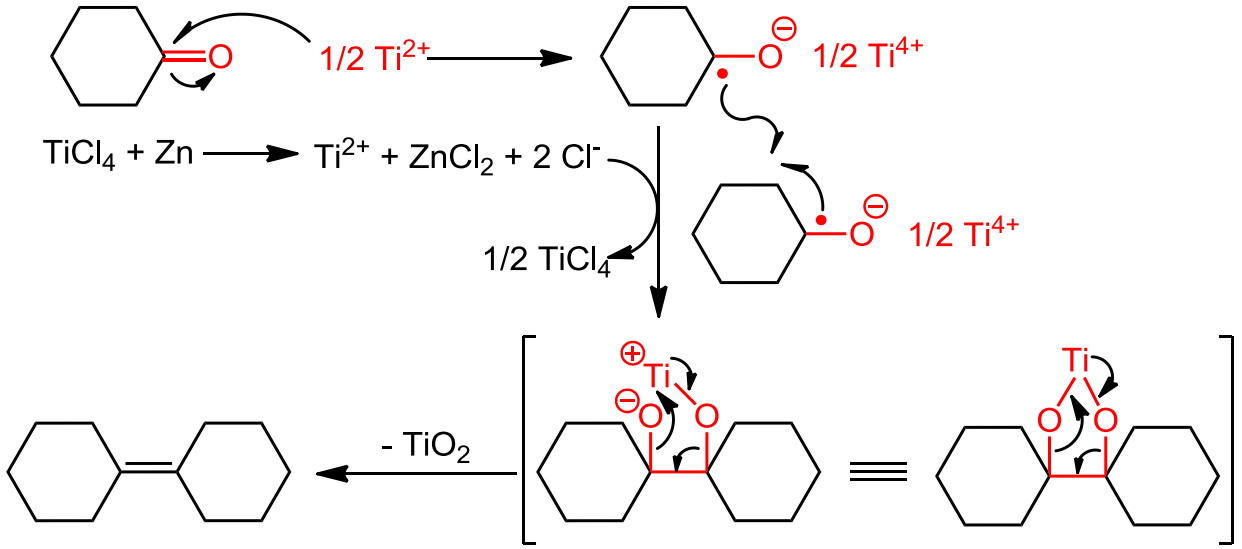




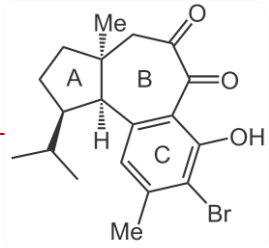
McMurry Reaction

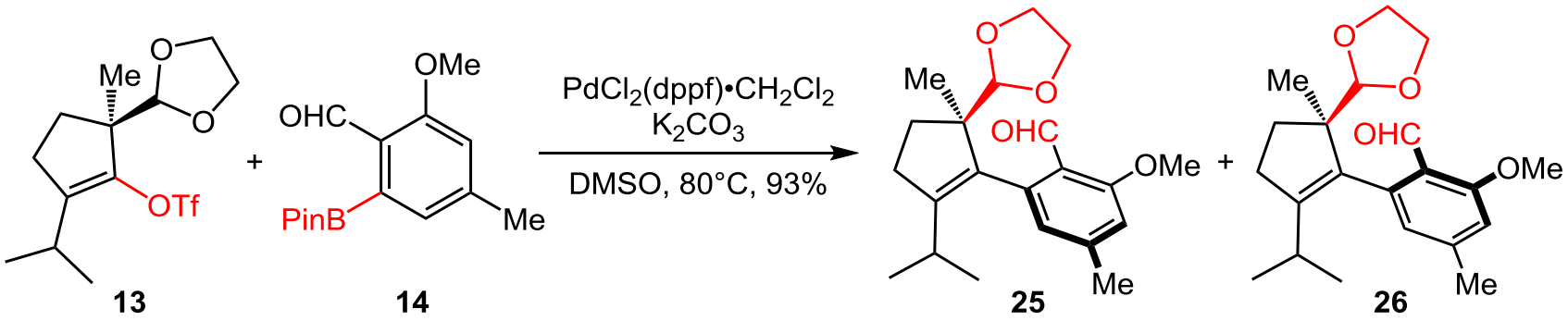
Two ketone or aldehyde groups are coupled to an alkene using titanium chloride compound and a reducing agent.

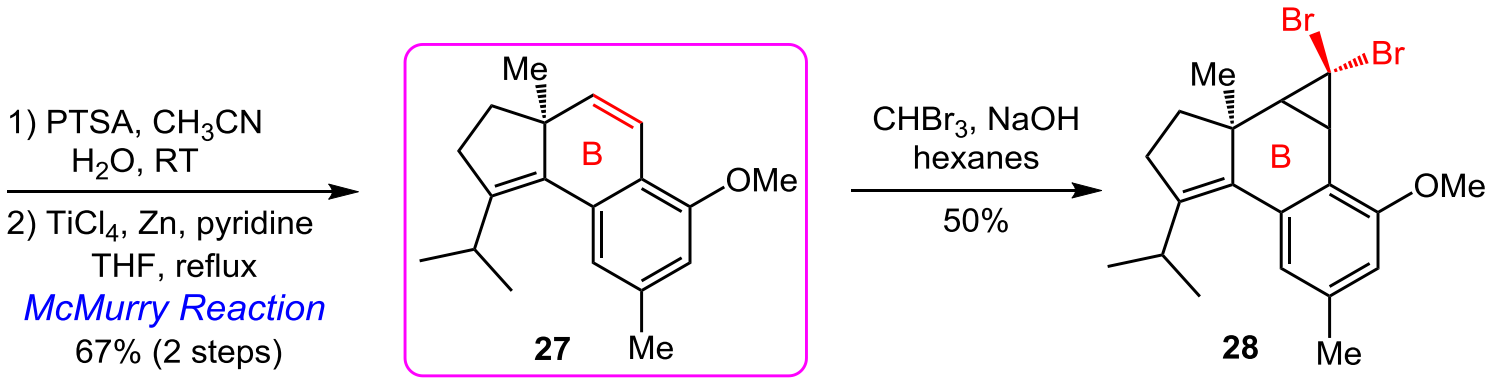




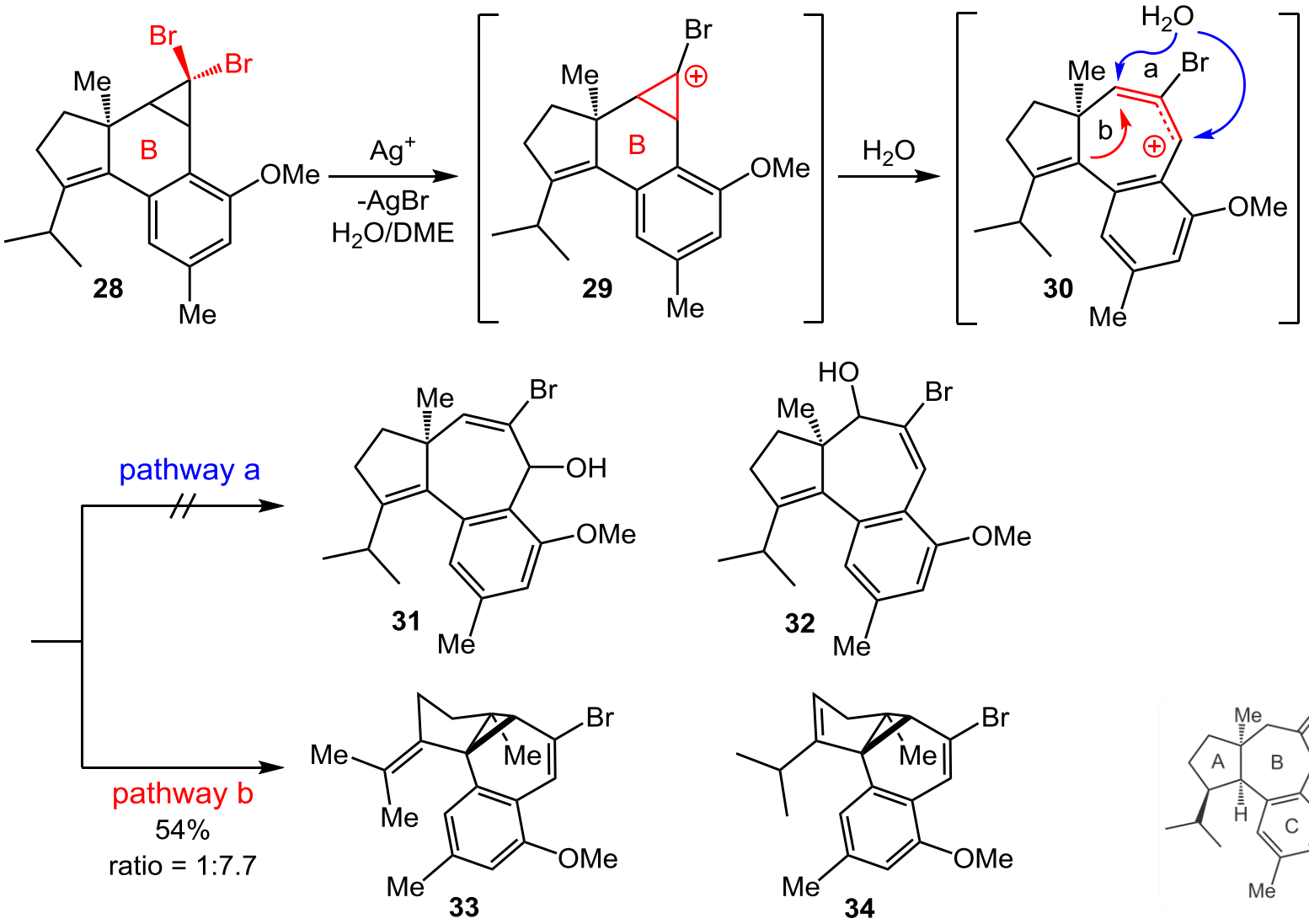
Attempt at the B ring expansion



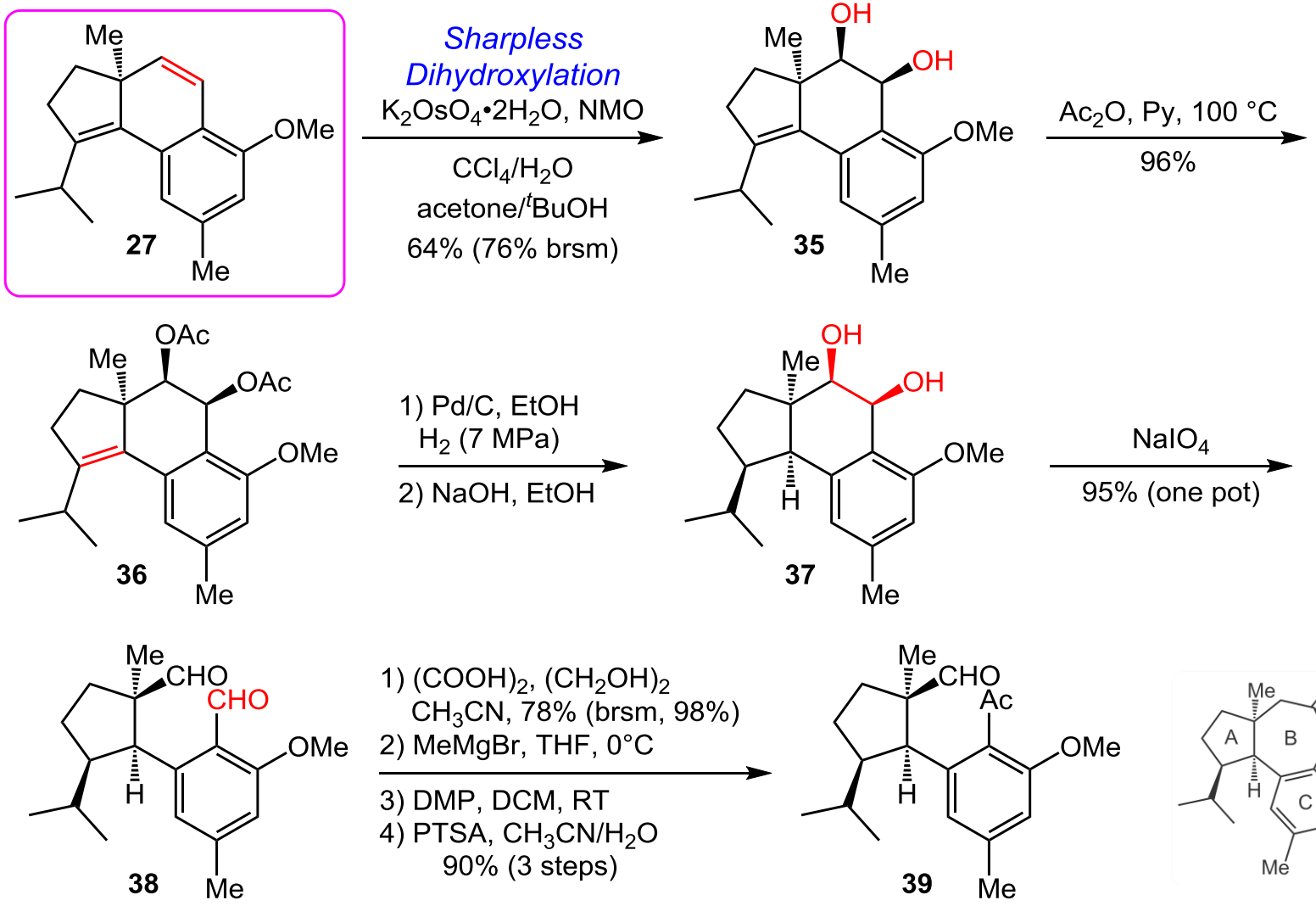




Undesired pathway

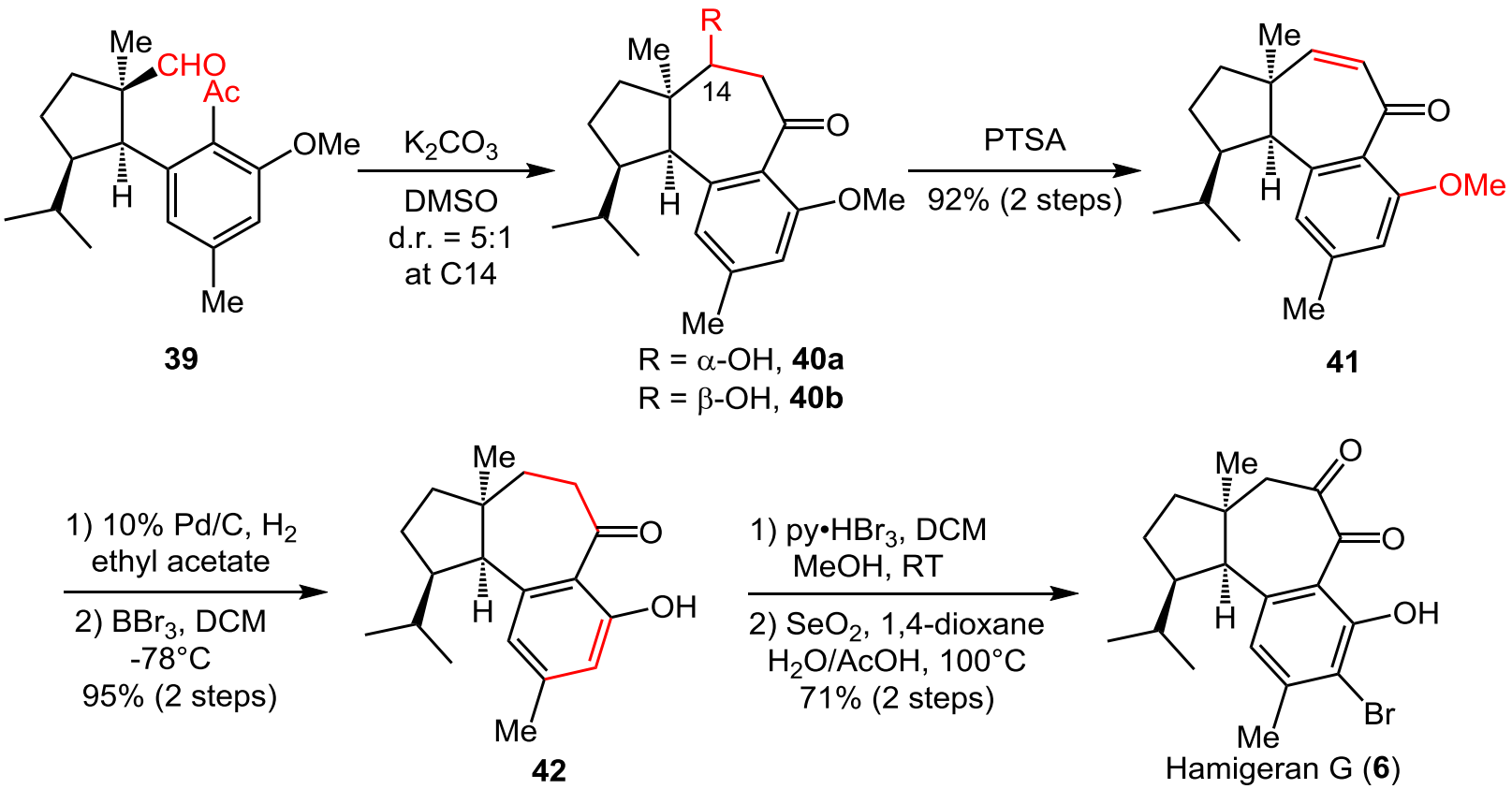


Total Synthesis of 6



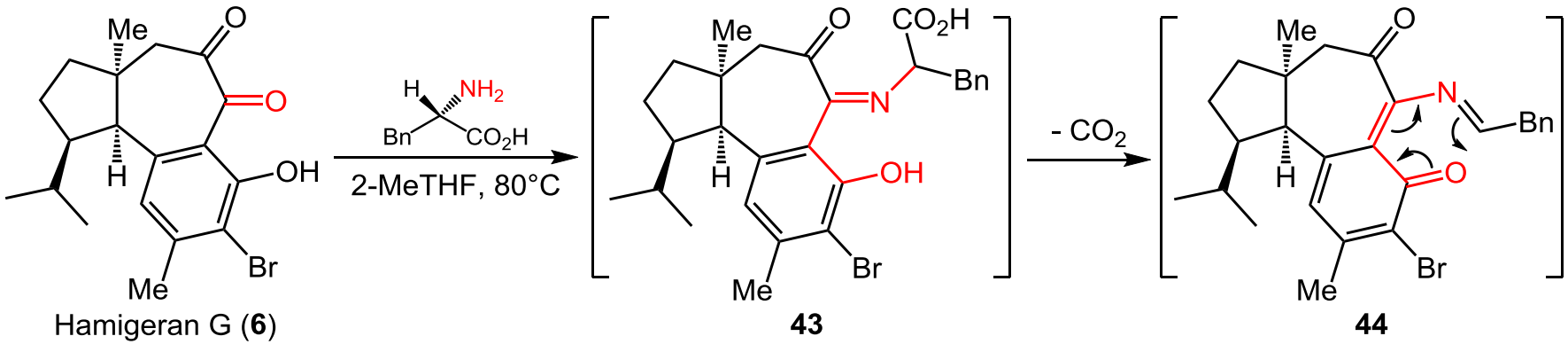
brsm: based on recovered starting material

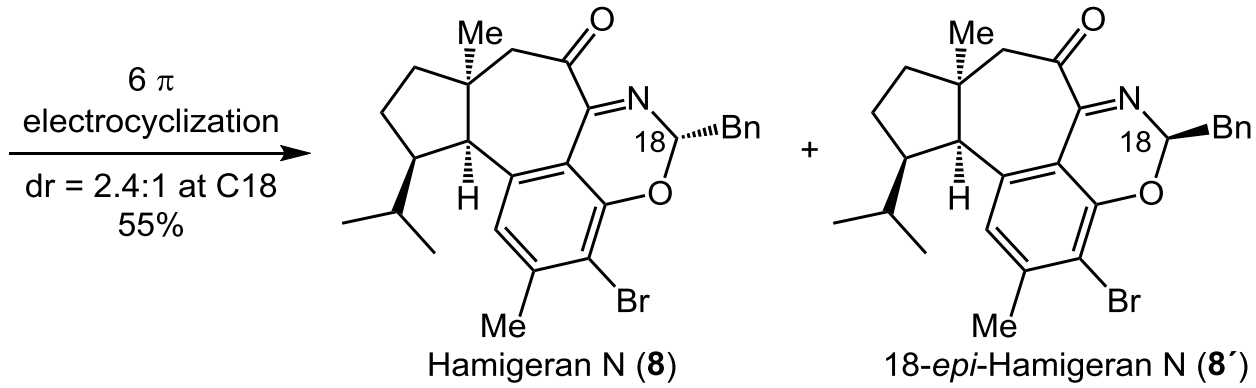
Total Synthesis of 6



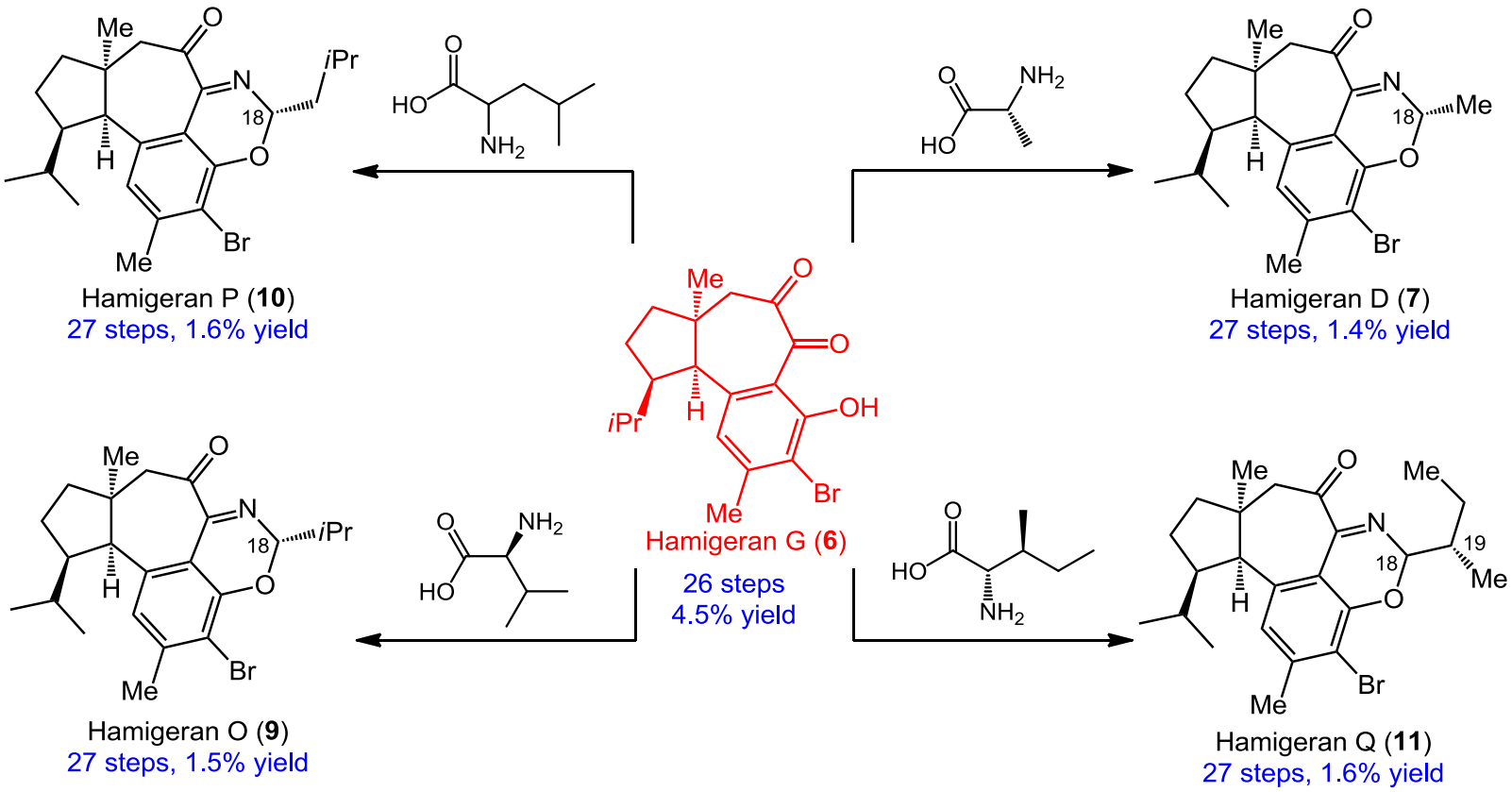
Biomimetric transformation of 6 into 8

The confirmation of Northcote's hypothesis

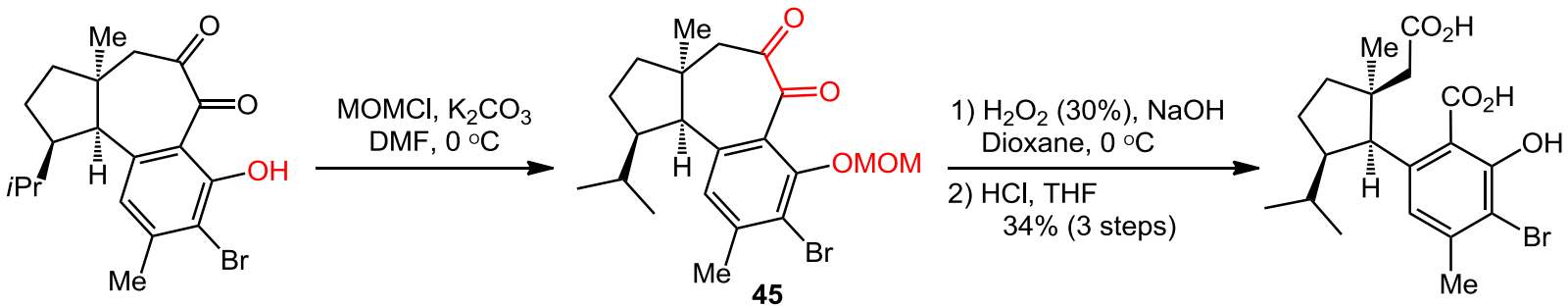




Divergent synthesis of Hamigerans



Divergent synthesis of Hamigerans



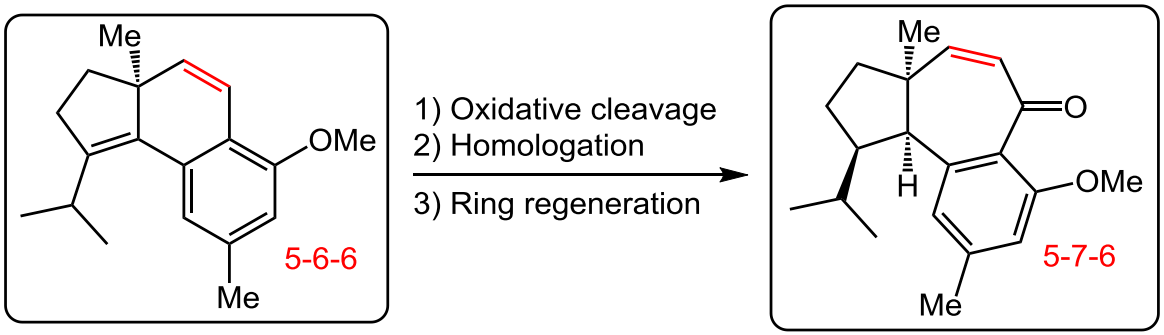
Hamigeran G (**6**)
26 steps, 4.5% yield

45

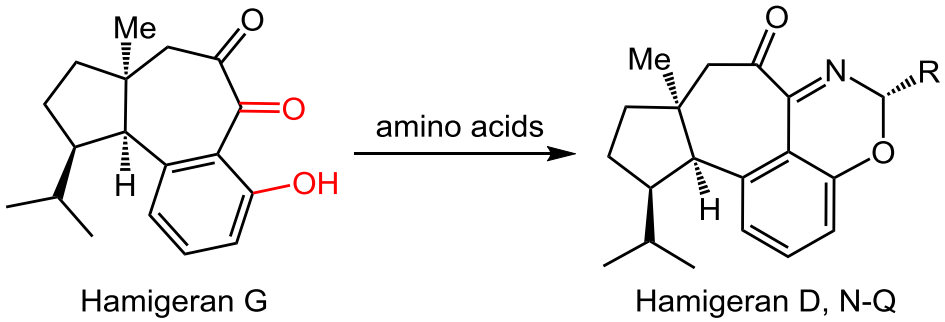
Hamigeran L (**4**)
29 steps, 1.5% yield

Summary

- The first total synthesis of Hamigeran L, G, D, and N-Q.
- This convergent synthetic strategy is based on the versatile common intermediate.



- The results suggest that Hamigeran D, and N-Q may derive from naturally occuring amino acids and Hamigeran G.



Hamigeran G

Hamigeran D, N-Q

The first paragraph

Hamigerans belong to a family of halogenated natural products isolated from the poecilosclerid sponge *Hamigera tarangaensis* and were discovered by Cambie and co-workers in 2000. More recent investigation of the same sponge by Northcote and co-workers led to the isolation of several new hamigerans, particularly the nitrogenous congeners hamigeran D and N–Q. To date, over 30 hamigerans have been discovered and identified, and most of them show interesting biological activities. Notably, hamigeran B completely inhibits replication of herpes and poliovirus in vitro without showing any significant cytotoxicity. Hamigeran G inhibits growth of the P388 tumor cell line as well as the HL-60 promyelocytic leukemia cell line (IC_{50} 8 μM).

The first paragraph

We have noticed that Hamigerans and gukulenins, a small group of marine tetraterpenoids from the Korean sponge *Phorbas gukulensis*, have similar structural features. Gukulenins contain unusual bis(tropolone) fragments, and gukulenins A and B inhibit growth of human colon, renal, pharynx, and stomach cancer cell lines with nanomolar IC_{50} values.

The last paragraph

In summary, we have accomplished the first total synthesis of hamigerans L, G, D, and N–Q. A convergent synthetic strategy was developed based on the versatile common intermediate **27**. Our results suggest that benzoxazine-containing **7** and **8–11** may derive from naturally occurring amino acids and **6**. We believe that this biomimetic approach should enable the synthesis of a variety of hamigerans and their derivatives, thus facilitating biological studies of these promising natural products. We are currently studying the total synthesis of the gukulenins.

Acknowledgement

Thanks
for your attention