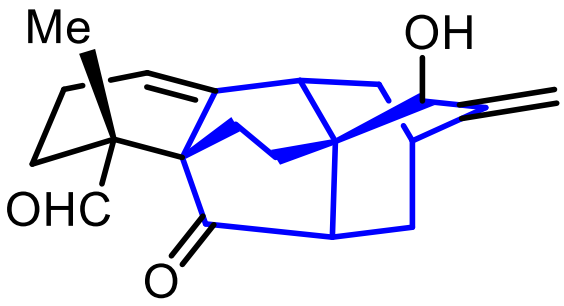
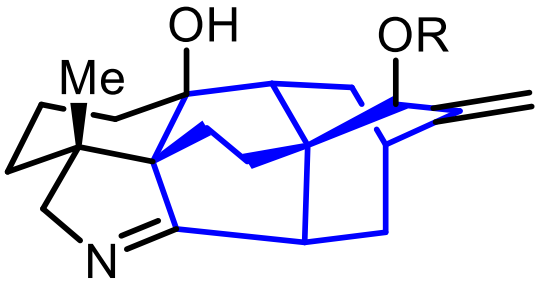
Total Synthesis of Atropurpuran and Arcutines



Atropurpuran



Arcutines

Student: Xuge Si
Supervisor: Prof. Quan Cai

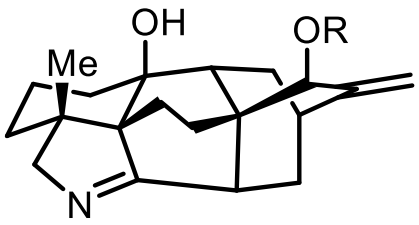
Contents

Contents

Aconitum arcuatum Maxim
（弯枝乌头）

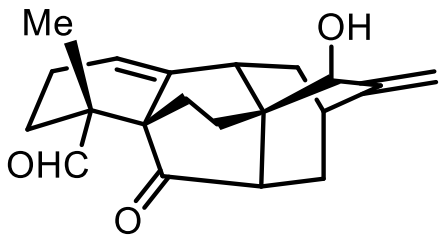
Aconitum: important medicinal plant;

Diterpenoid alkaloids:
the characteristic active components;
strong toxicity and broad biological activities;
with complex and diverse skeletons;



Arcutine; R = (*S*)-*s*BuCO
Arcutinine; R = *i*PrO
Arcutinidine; R = H

Bassonova (2000, 2001)



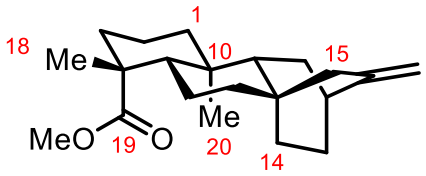
Atropurpuran

Wang (2009)

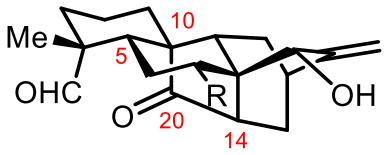
Aconitum hemsleyanum
（瓜叶乌头）

Tashkhodzhaev, B.; Saidkhodzhaeva, S. A.; Bessonova, I. A.; Antipin, M. Y. *Chem. Nat. Compd.* **2000**, *36*, 79.
Saidkhodzhaeva, S. A.; Bessonova, I. A.; Abdullaev, N. D. *Chem. Nat. Compd.* **2001**, *37*, 466.
Tang, P.; Chen, Q.-H.; Wang, F.-P. *Tetrahedron Lett.* **2009**, *50*, 460.

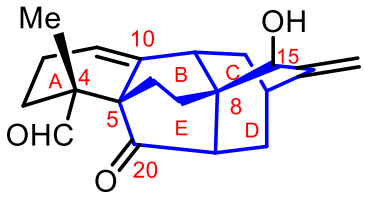
Typical C_{20}-diterpenoids and diterpenoid alkaloids:

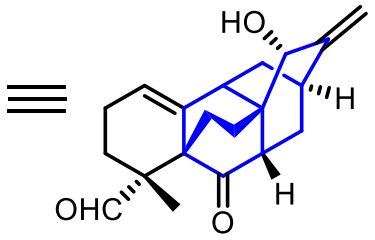


Methyl atisenoate
(atisane type)

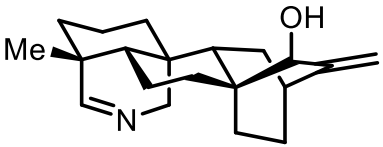


Canpylopin(R=OAc)
(hetidane type)

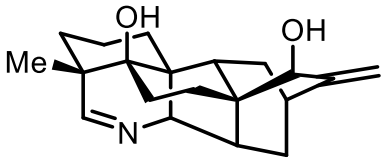




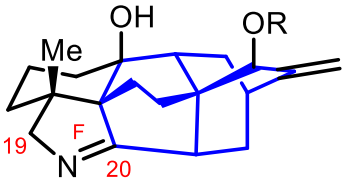
Atropurpuran
(arcutane type)



Isoazitine
(atisine type)



Tongolinene
(hetidine type)

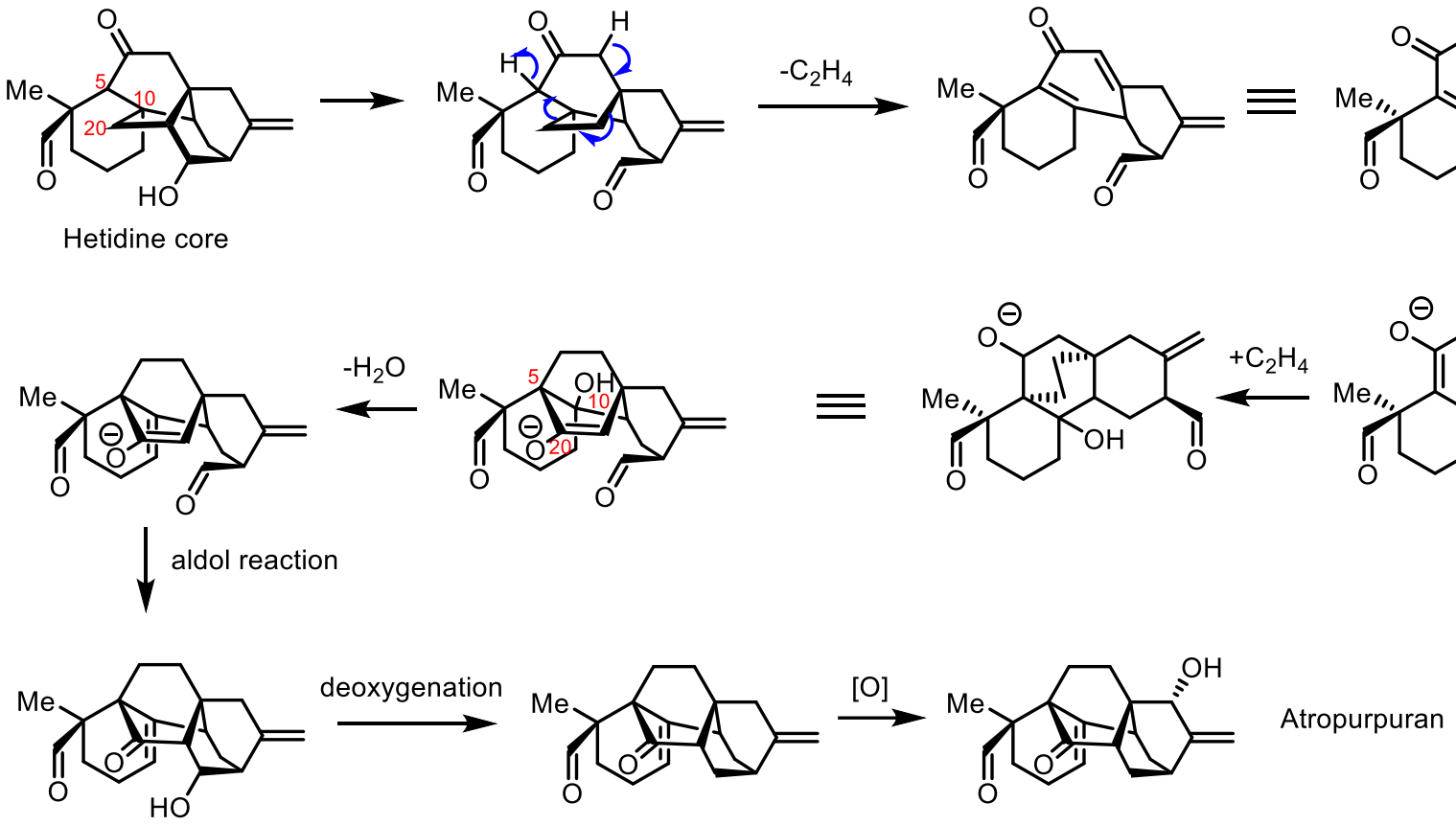


Arcutinine(R=*i*PrO)
(arcutine type)

Challenges: doubly fused bicycle[2.2.2]octane moieties (cage-like skeleton);
multiple stereogenic centres (three all-carbon quaternary centres);
a congested pyrroline motif (for arcutines).

Contents

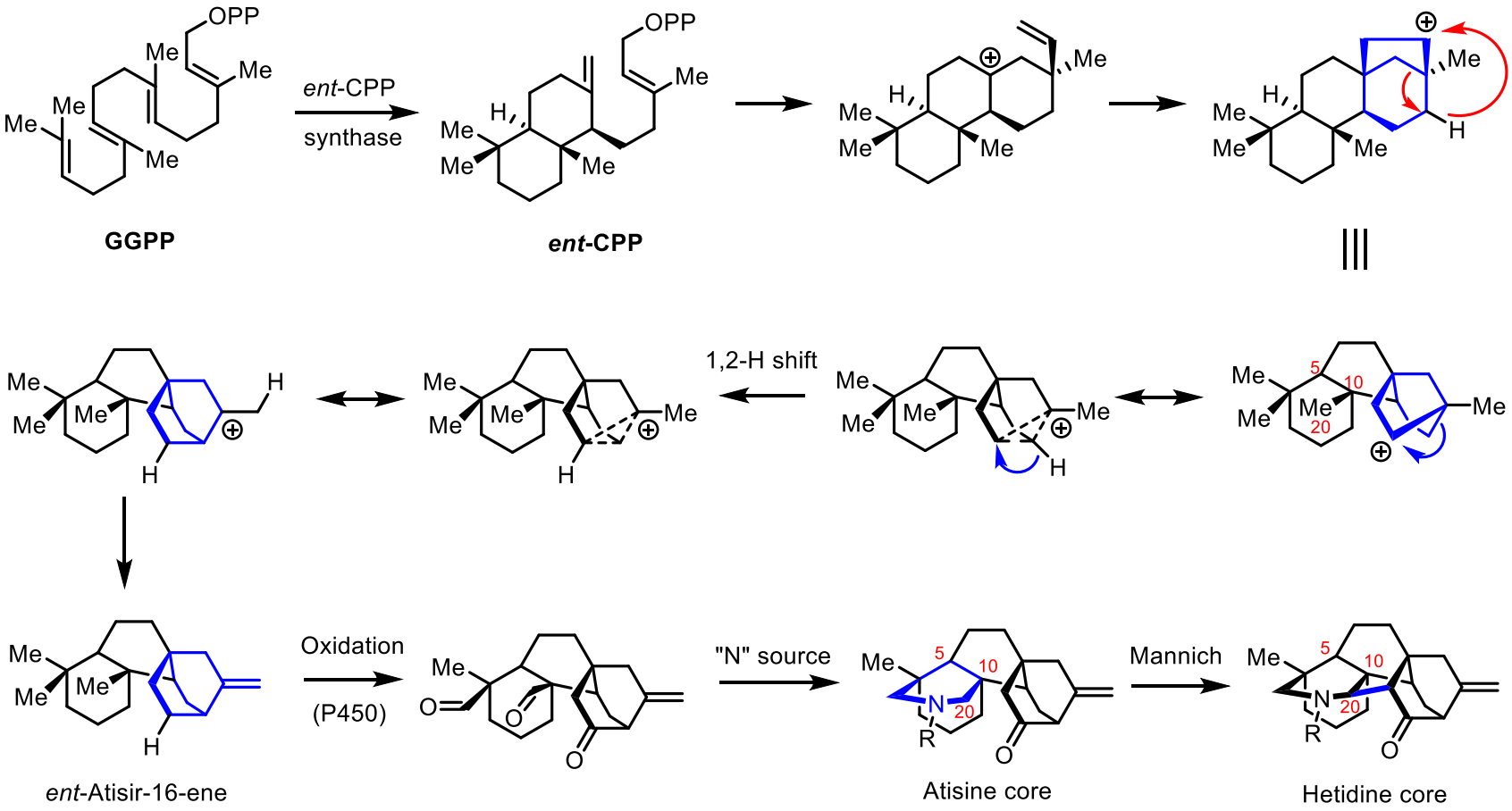
Proposed biosynthesis of atropurpuran by Wang:



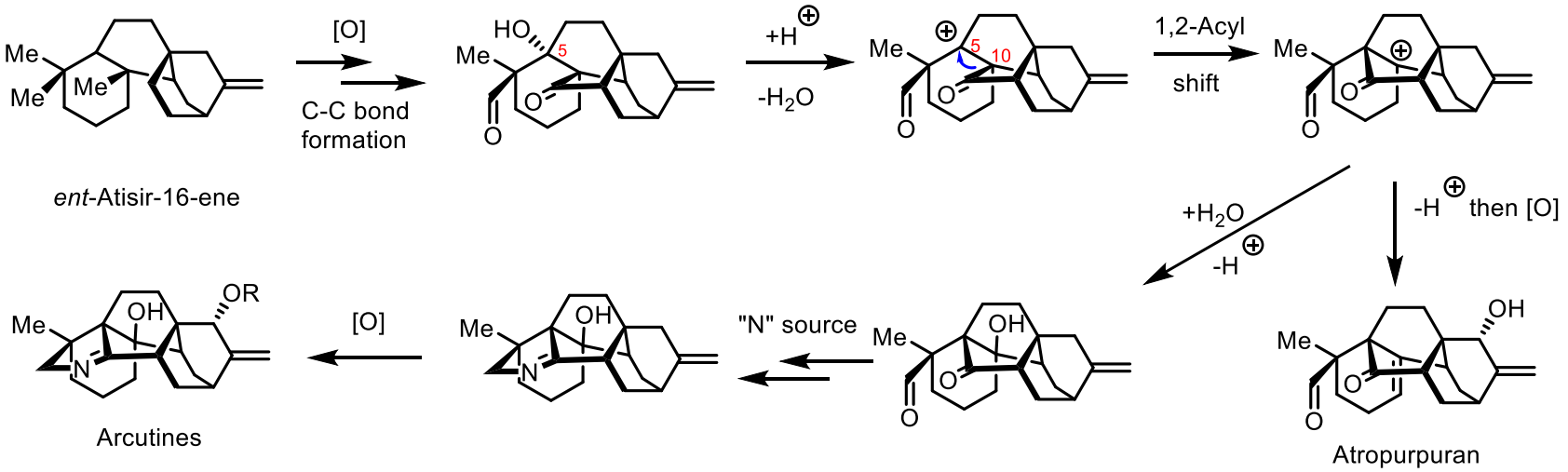
But Sarpong thinks it's unlikely.

Tang, P.; Chen, Q.-H.; Wang, F.-P. *Tetrahedron Lett.* **2009**, *50*, 460.

General biosynthesis of C_{20}-diterpenoid alkaloids:

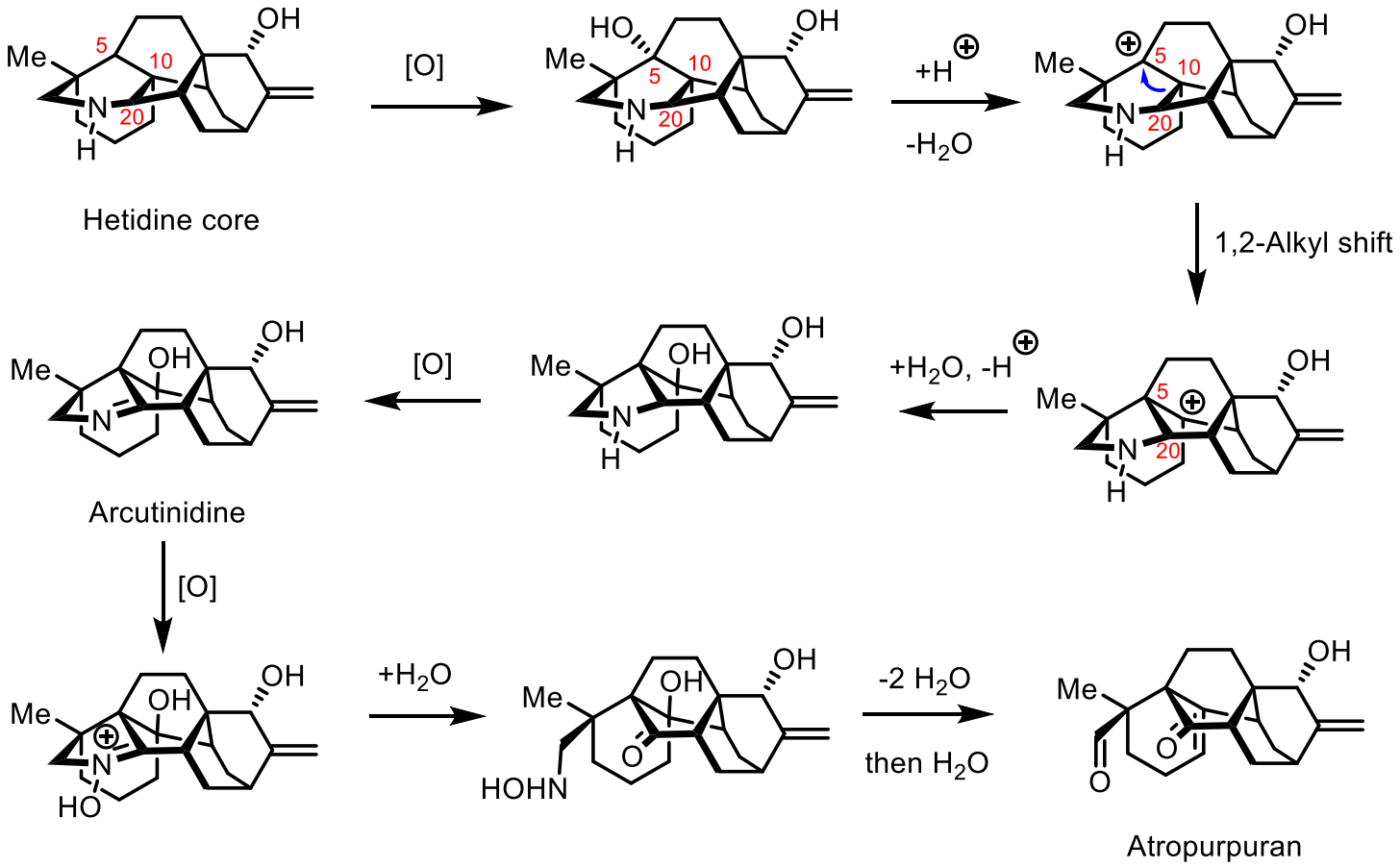


Biosynthesis proposed by Sarpong – 1,2-Acyl Rearrangement



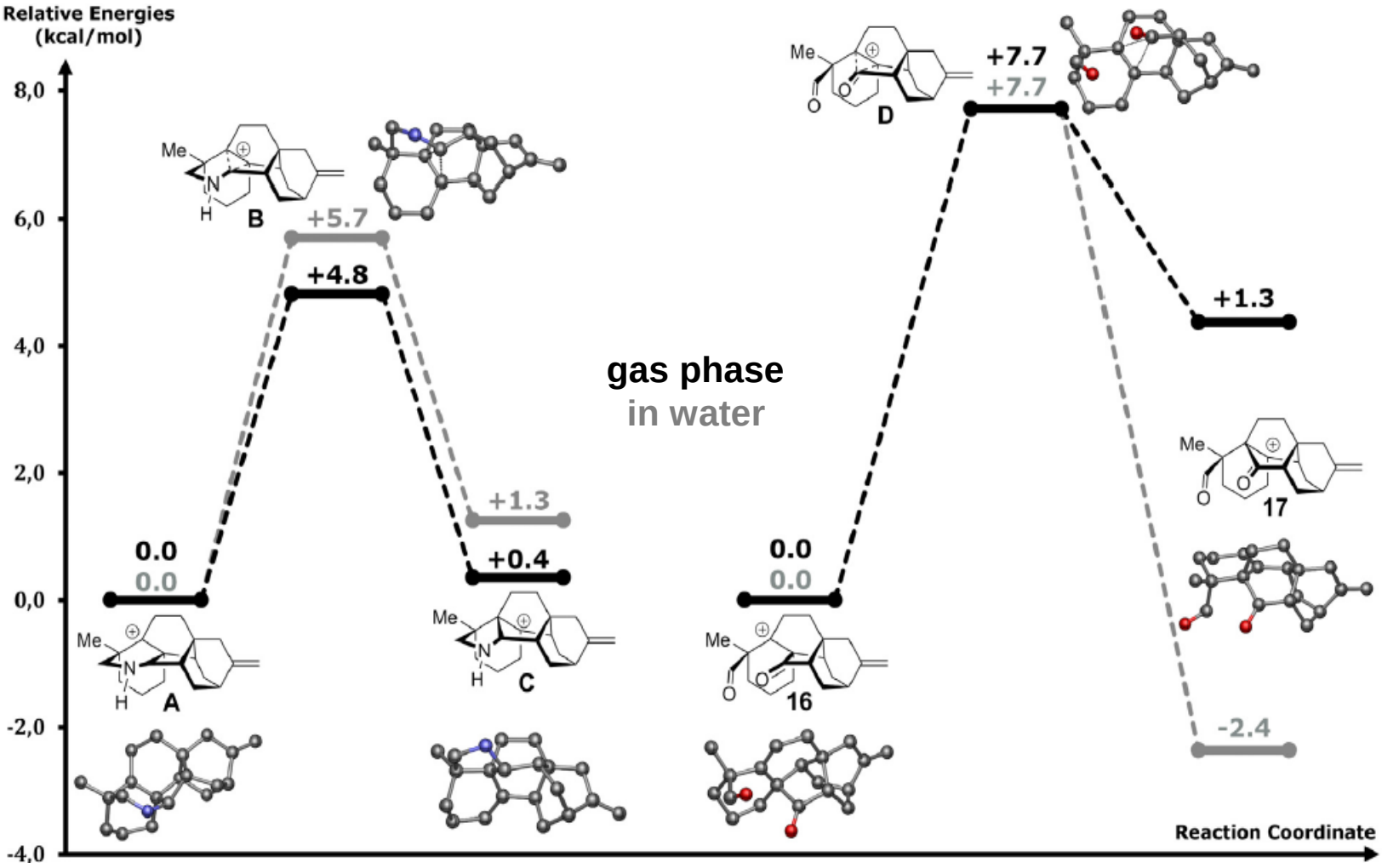
Weber, M.; Owens, K.; Sarpong, R. *Tetrahedron Lett.* **2015**, *56*, 3600.

Biosynthesis proposed by Sarpong – 1,2-Alkyl Rearrangement



Weber, M.; Owens, K.; Sarpong, R. *Tetrahedron Lett.* **2015**, *56*, 3600.

Which one is more possible?



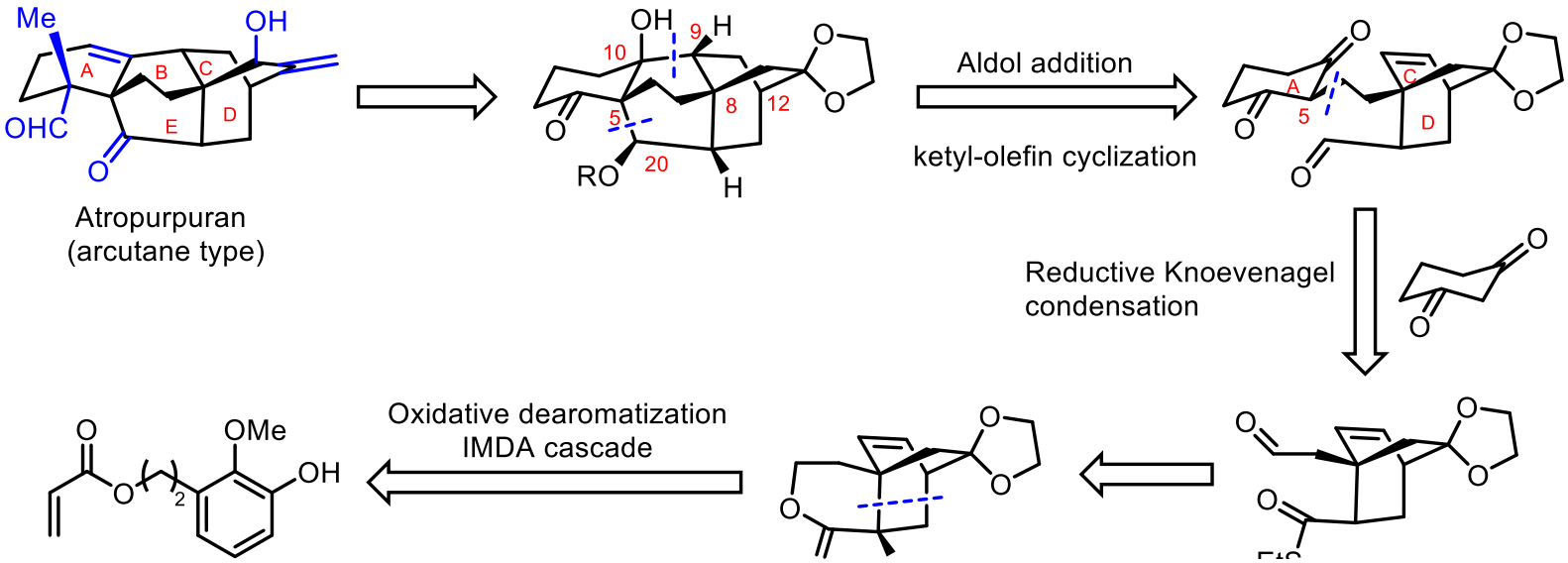
-2.1 kcal/mol energy release with –OH migration.

Weber, M.; Owens, K.; Sarpong, R. *Tetrahedron Lett.* **2015**, *56*, 3600.

Contents

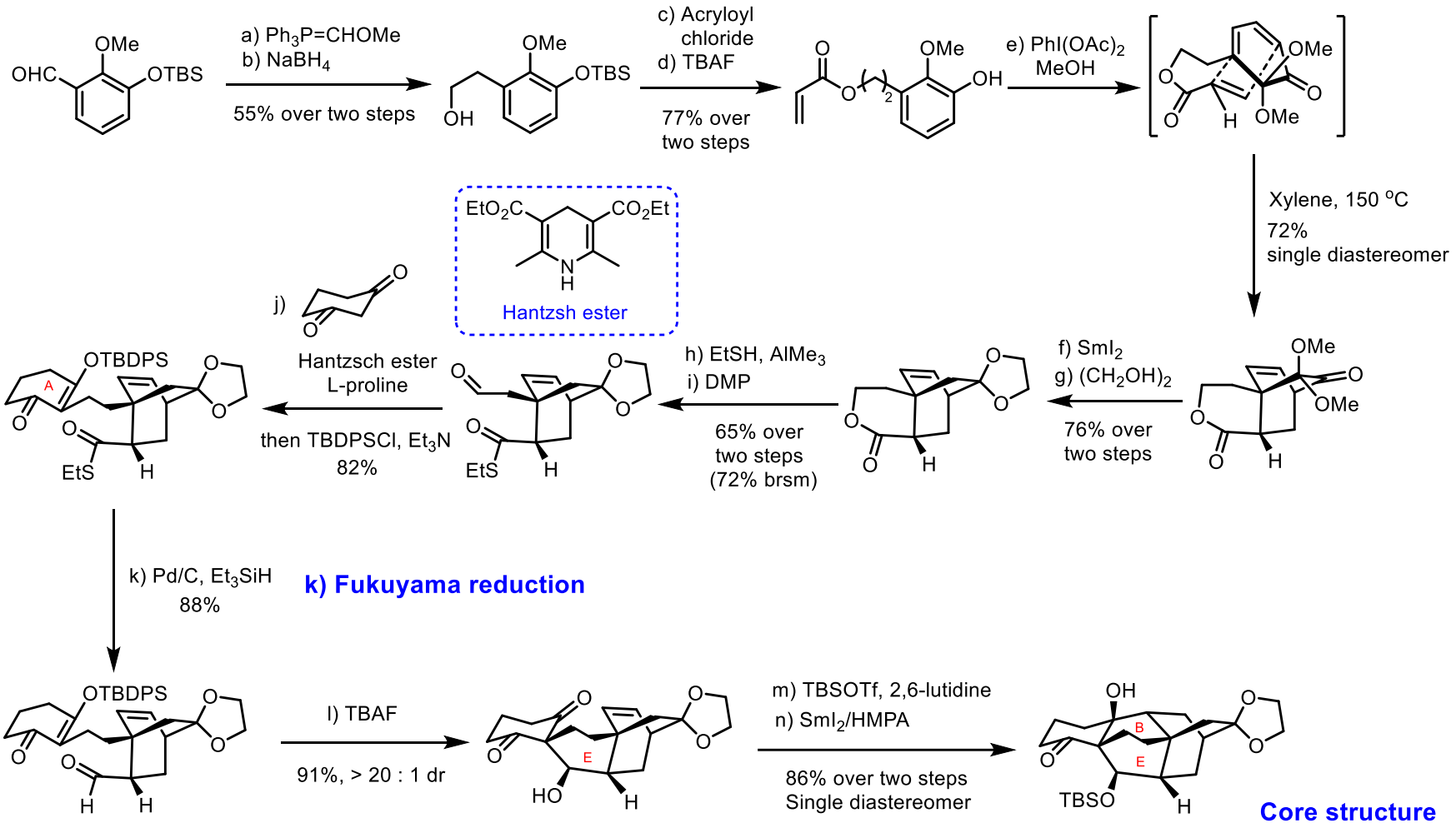
II Total Synthesis of Atropurpuran (the First Total Synthesis)

Qin's design:



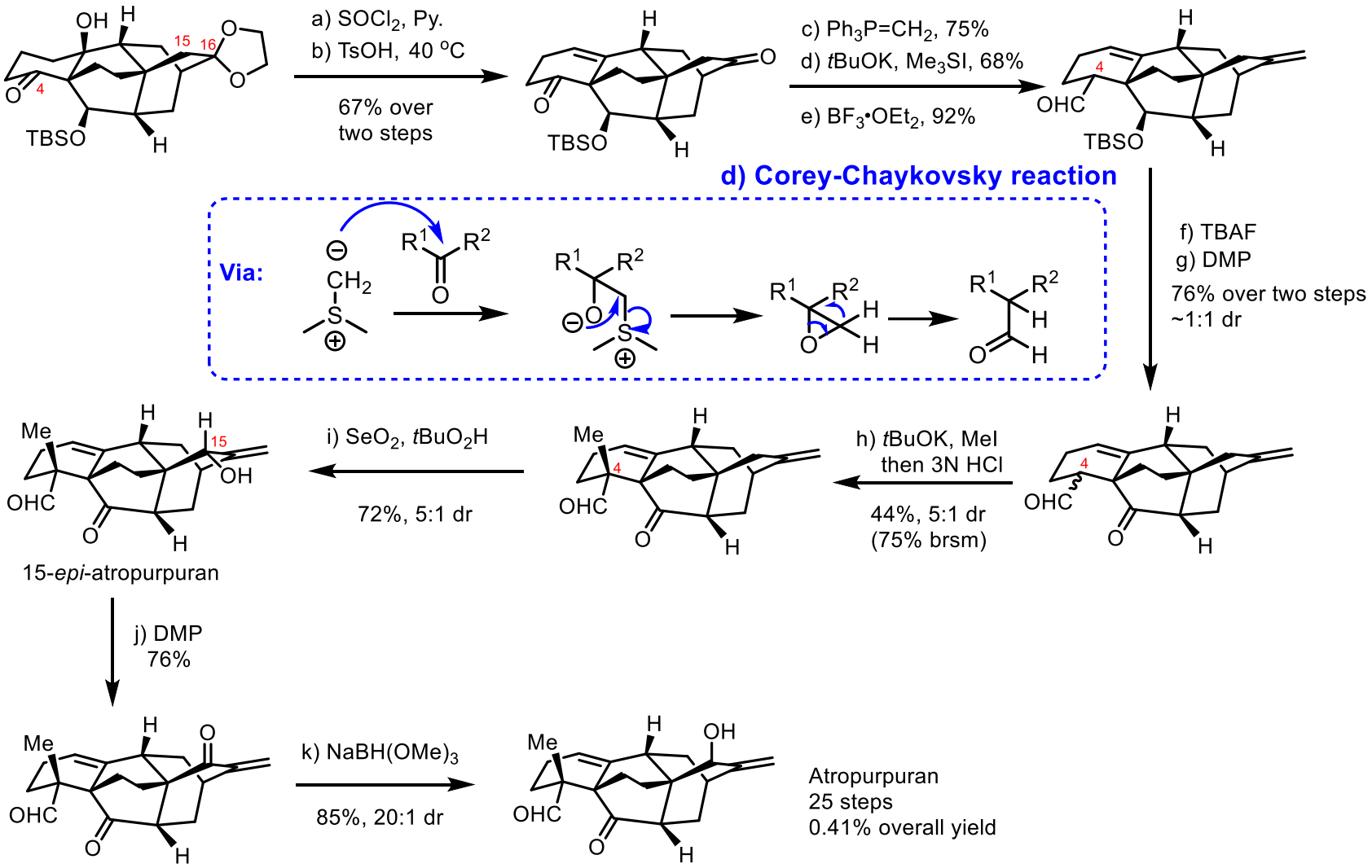
Gong, J.; Chen, H.; Liu, X.-Y.; Wang, Z.-X.; Nie, W.; Qin, Y. *Nat. Commum*. **2016**, *7*, 12183.

II Total Synthesis of Atropurpuran (the First Total Synthesis)



Gong, J.; Chen, H.; Liu, X.-Y.; Wang, Z.-X.; Nie, W.; Qin, Y. *Nat. Commum*. **2016**, *7*, 12183.

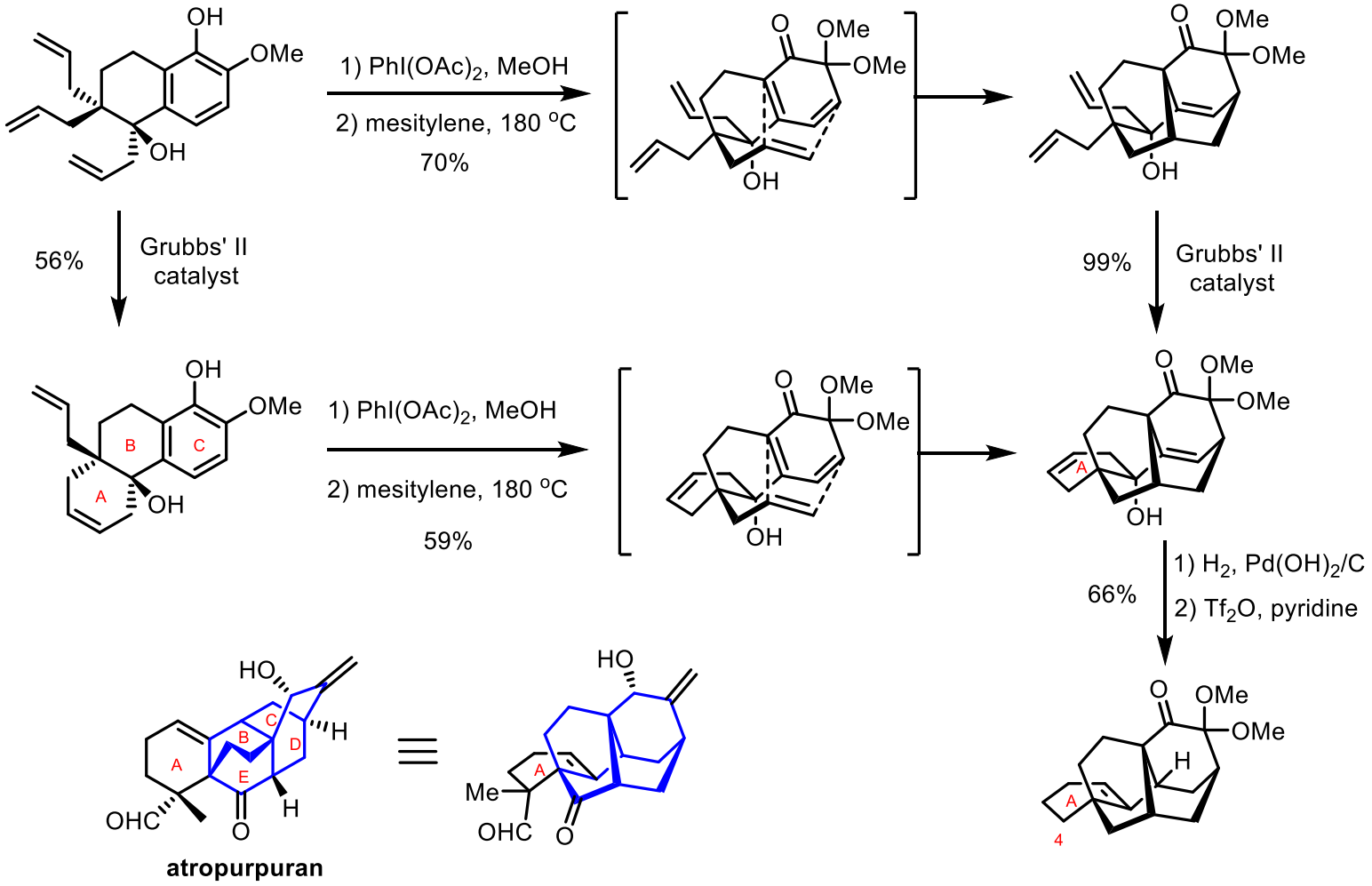
II Total Synthesis of Atropurpuran (the First Total Synthesis)



Gong, J.; Chen, H.; Liu, X.-Y.; Wang, Z.-X.; Nie, W.; Qin, Y. *Nat. Commum*. **2016**, *7*, 12183.

II Total Synthesis of Atropurpuran (by Xu)

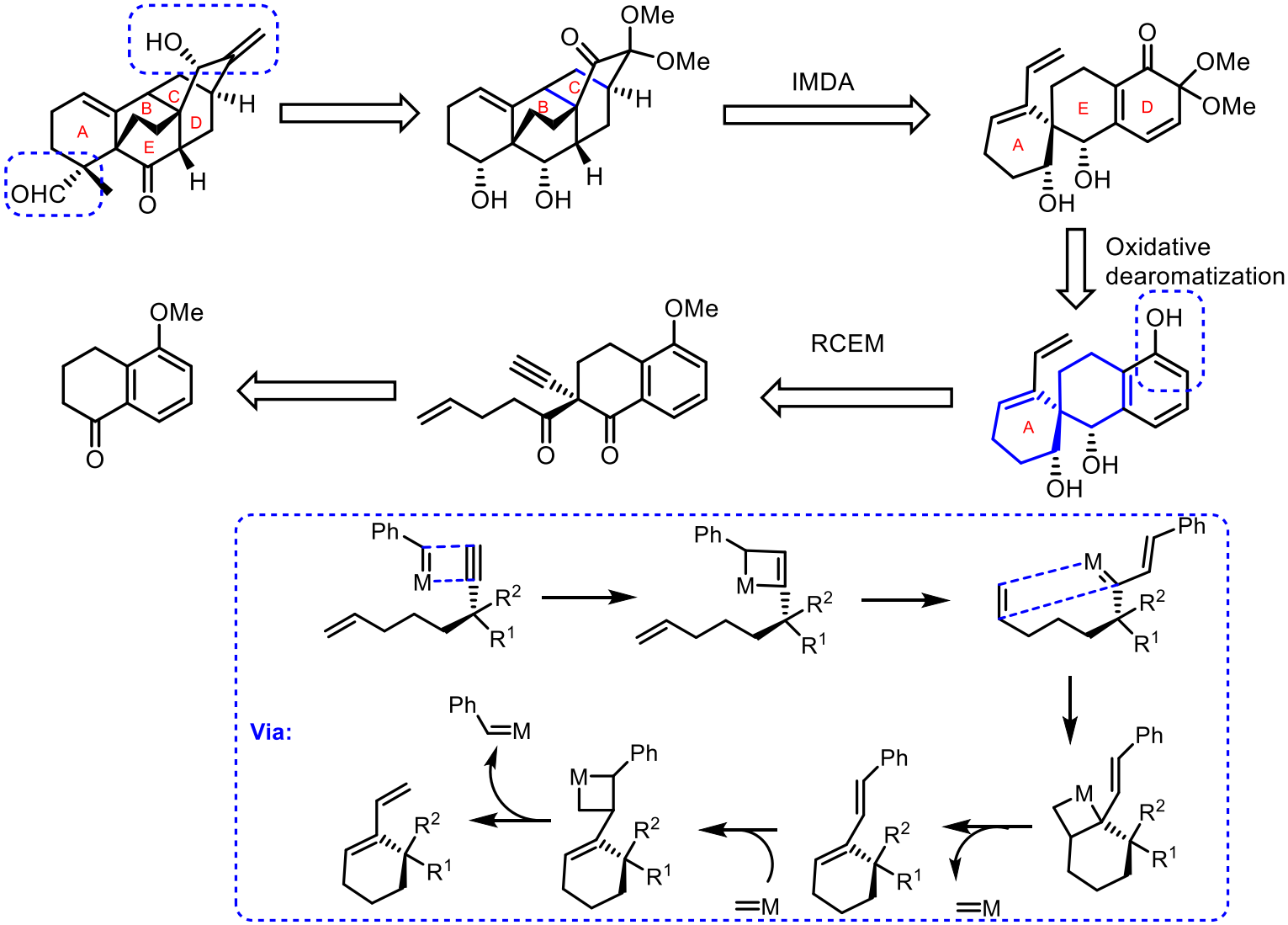
Kobayashi's synthetic study:



Suzuki, T.; Sasaki, A.; Egashira, N; Kobayashi, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9177.

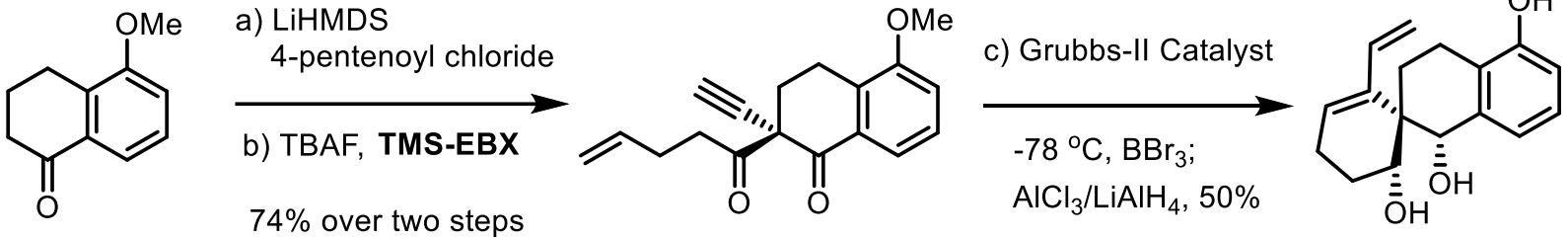
II Total Synthesis of Atropurpuran (by Xu)

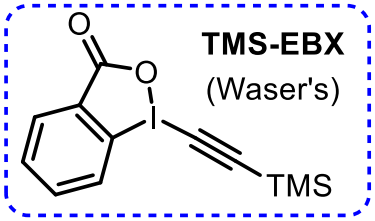
Xu's design:

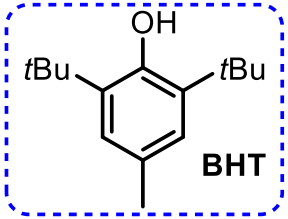


Xie, S.-L.; Chen, G.; Yan, H.; Hou, J.-P.; He, Y.-P.; Zhao, T.-Y.; Xu, J. *J. Am. Chem. Soc*. **2019**, *141*, 3435.

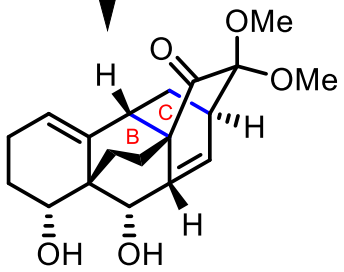
II Total Synthesis of Atropurpuran (by Xu)

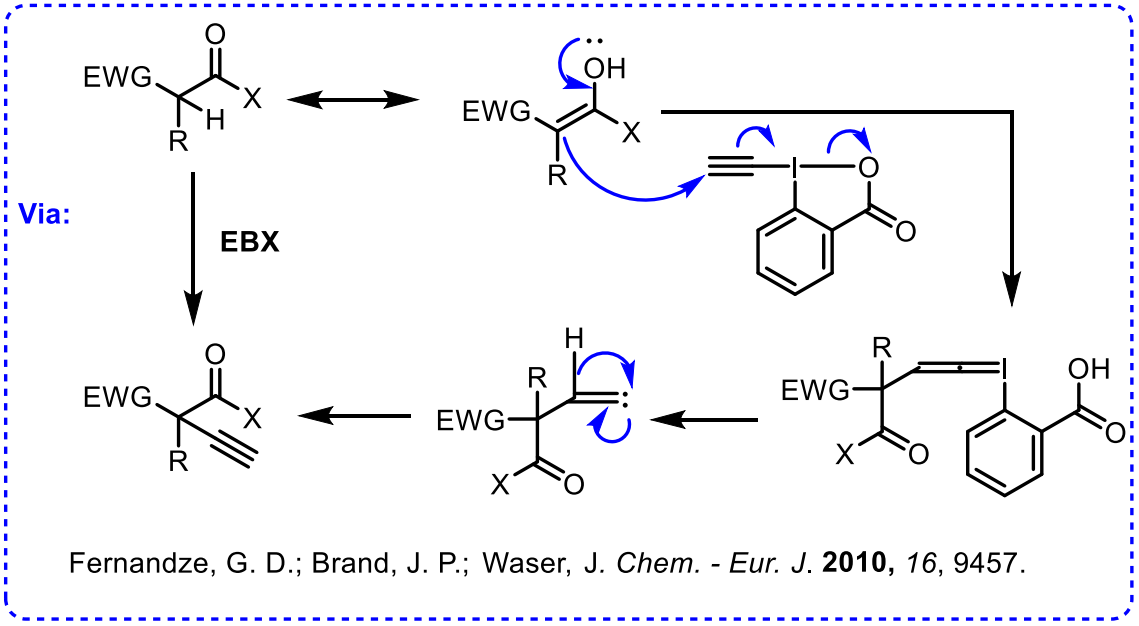




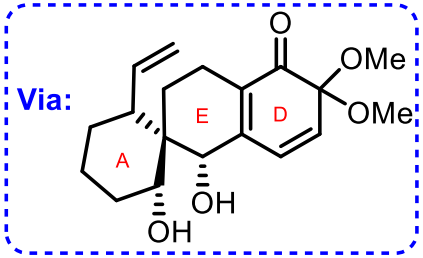


d) $PhI(OAc)_2$, MeOH;
BHT, mesitylene
160 °C, 55%

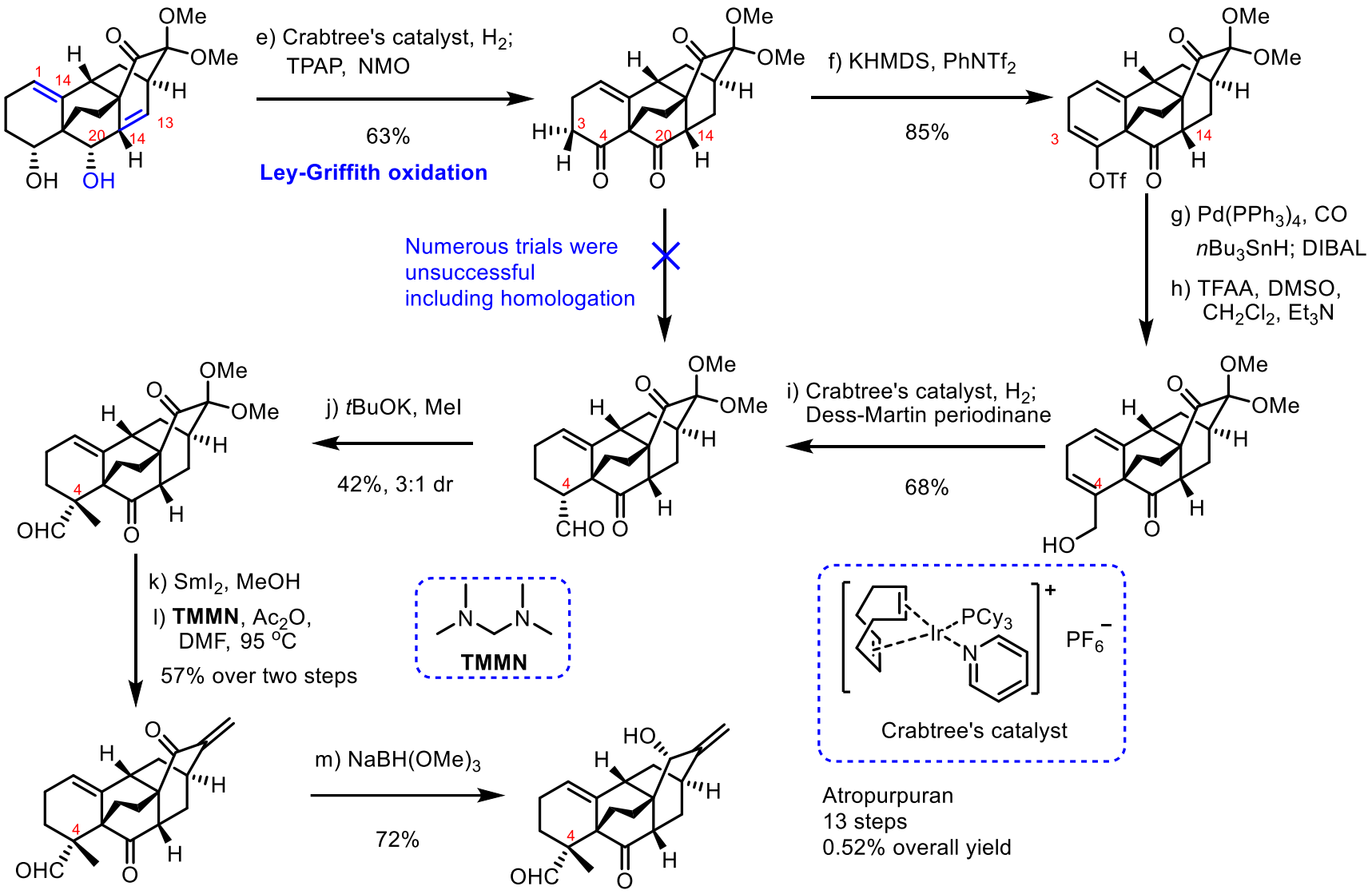




Fernandze, G. D.; Brand, J. P.; Waser, J. *Chem. - Eur. J.* **2010,** *16*, 9457.



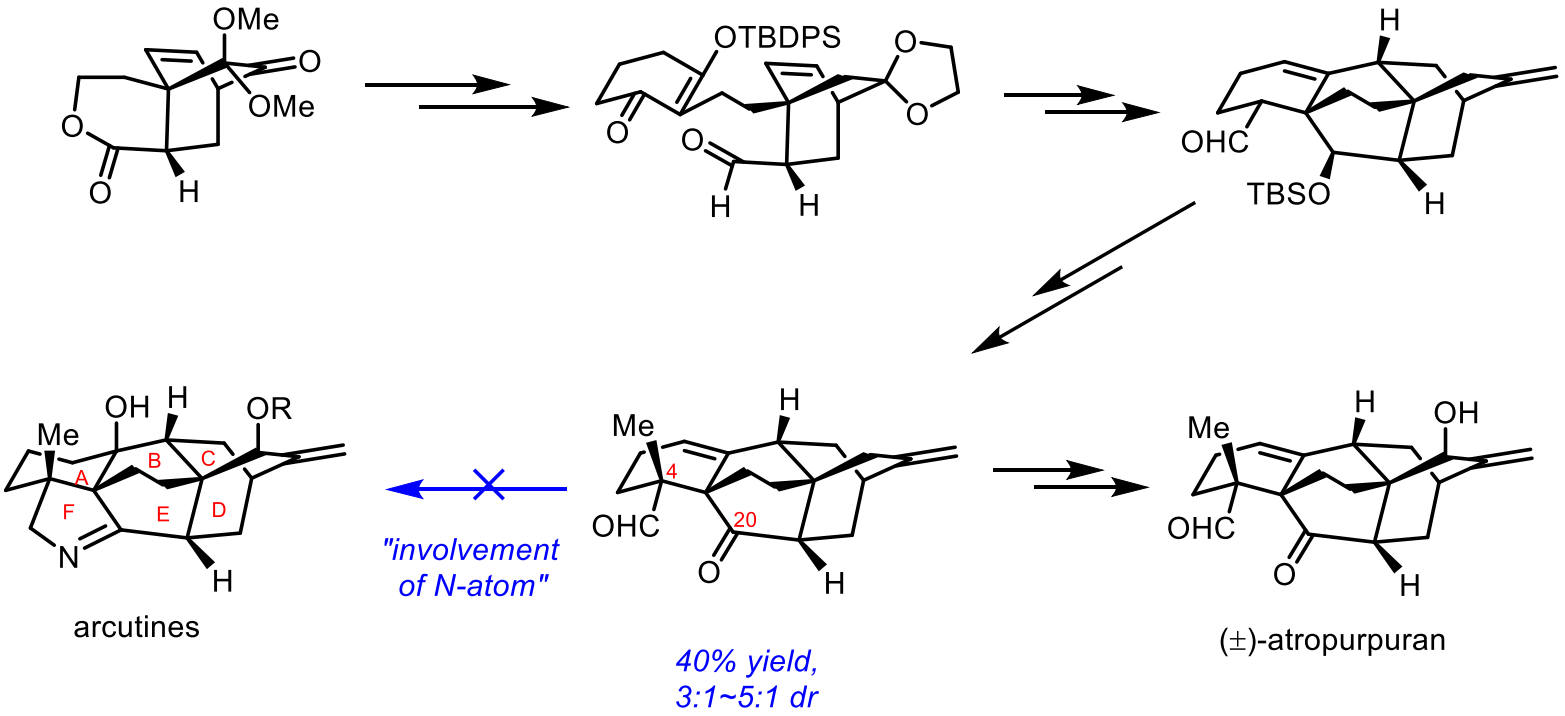
II Total Synthesis of Atropurpuran (by Xu)



Contents

III Total Synthesis of Arcutines (the First Total Synthesis)

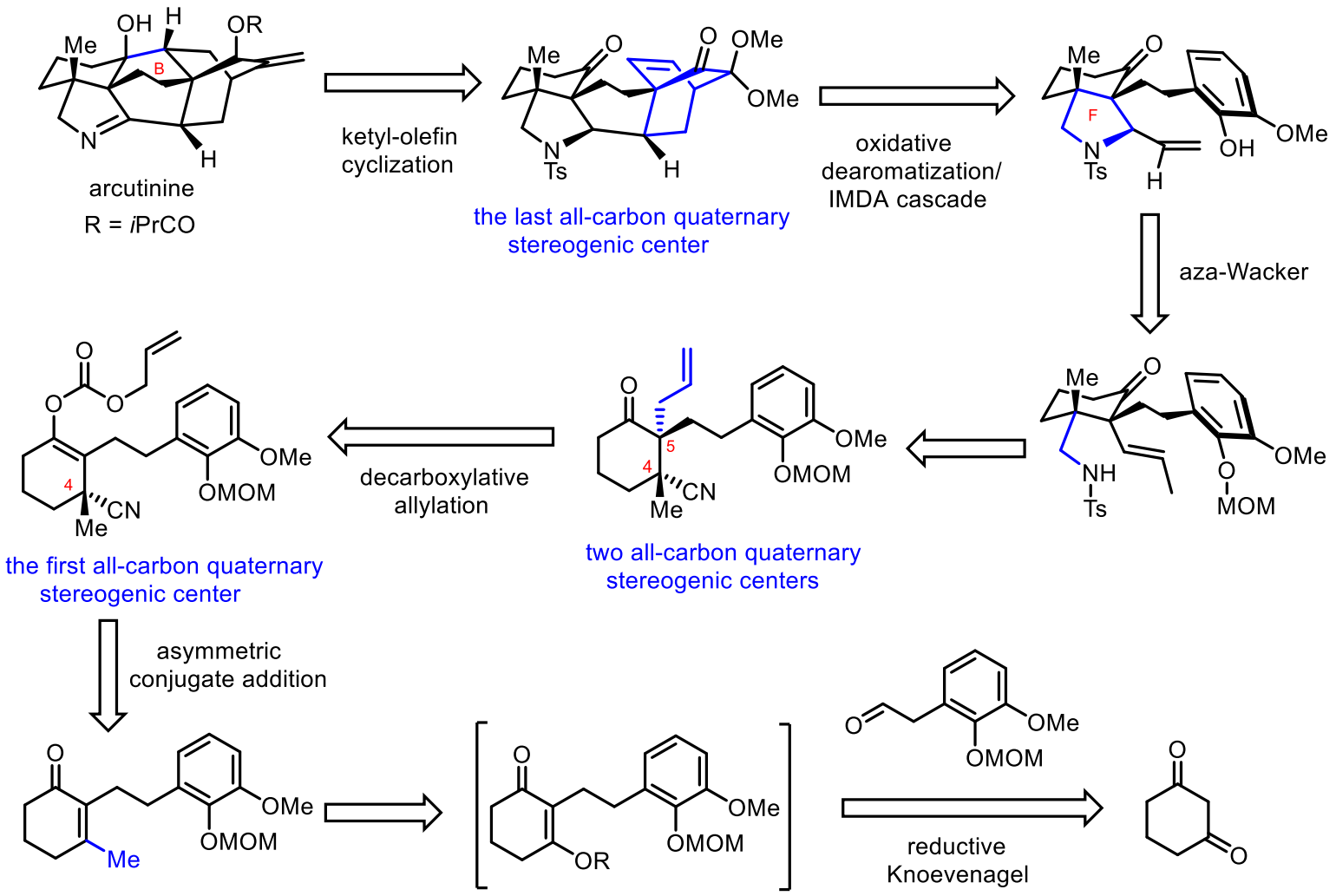
Can a reductive amination of atropurpuran lead to arcutines?



Nie, W.; Gong, J.; Chen, Z.-H.; Liu, J.-Z.; Tian, D.; Song, H.; Liu, X.-Y.; Qin, Y. *J. Am. Chem. Soc*. **2019**, *141*, 9712.

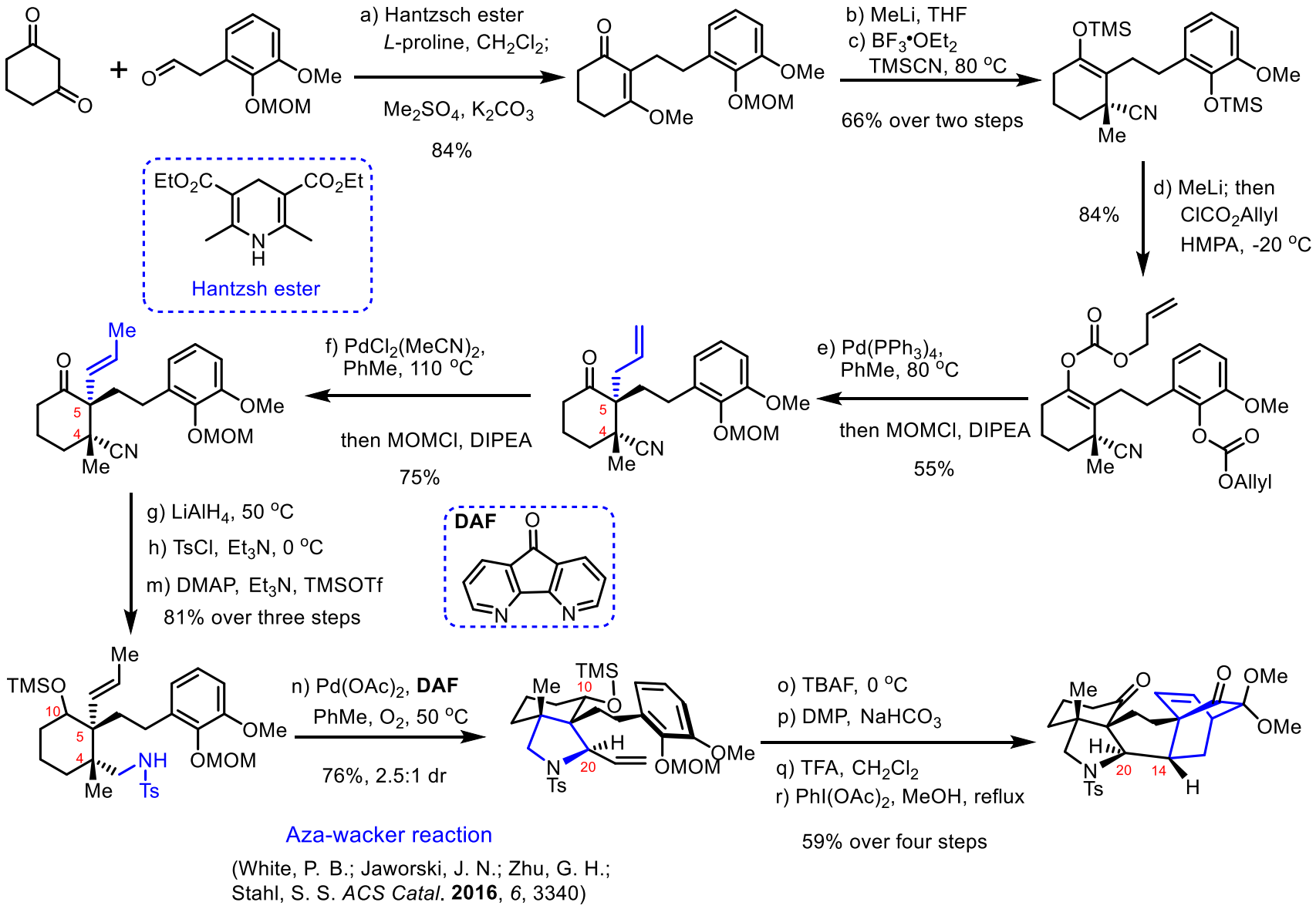
III Total Synthesis of Arcutines (the First Total Synthesis)

Qin's new design:

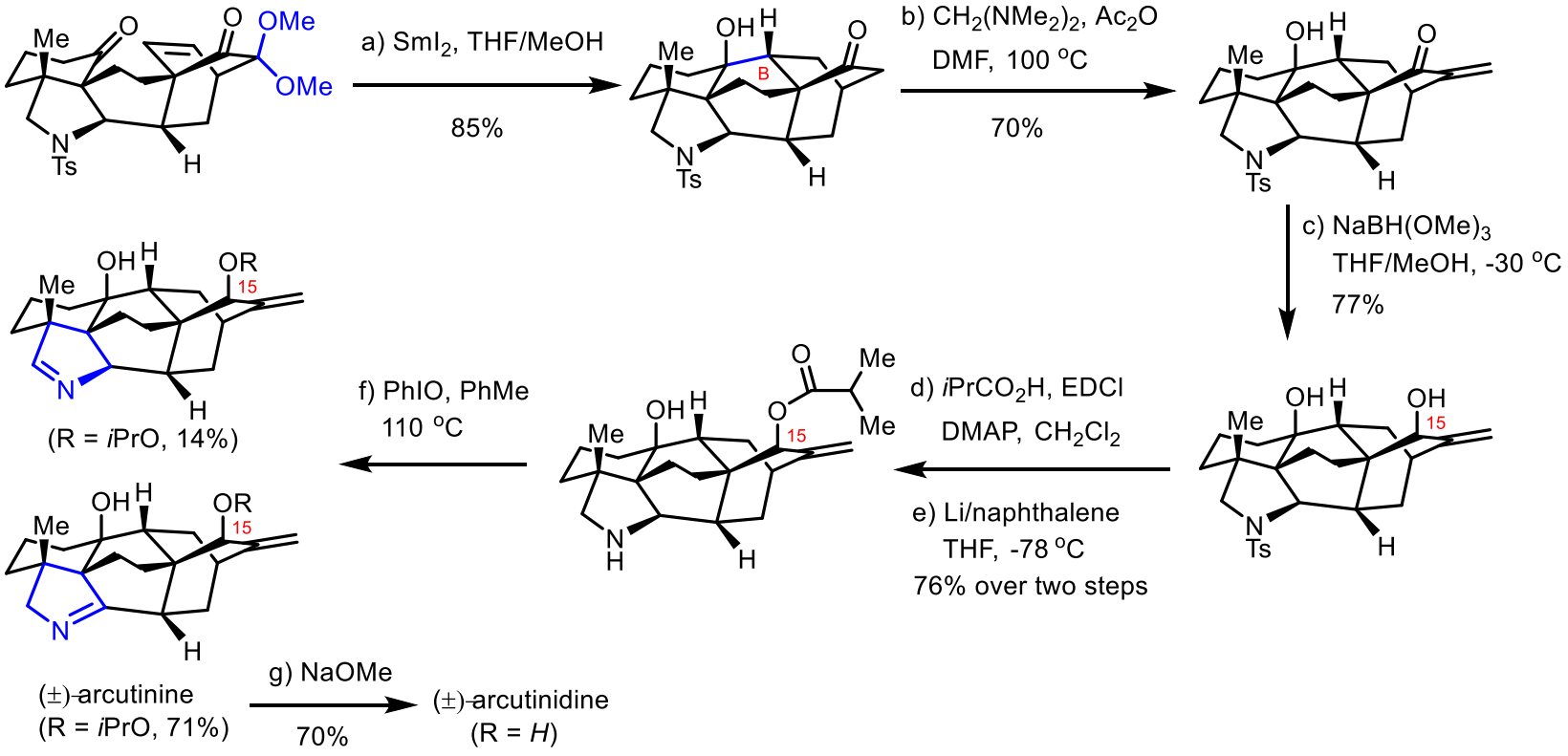


Nie, W.; Gong, J.; Chen, Z.-H.; Liu, J.-Z.; Tian, D.; Song, H.; Liu, X.-Y.; Qin, Y. *J. Am. Chem. Soc*. **2019**, *141*, 9712.

III Total Synthesis of Arcutines (the First Total Synthesis)



III Total Synthesis of Arcutines (the First Total Synthesis)



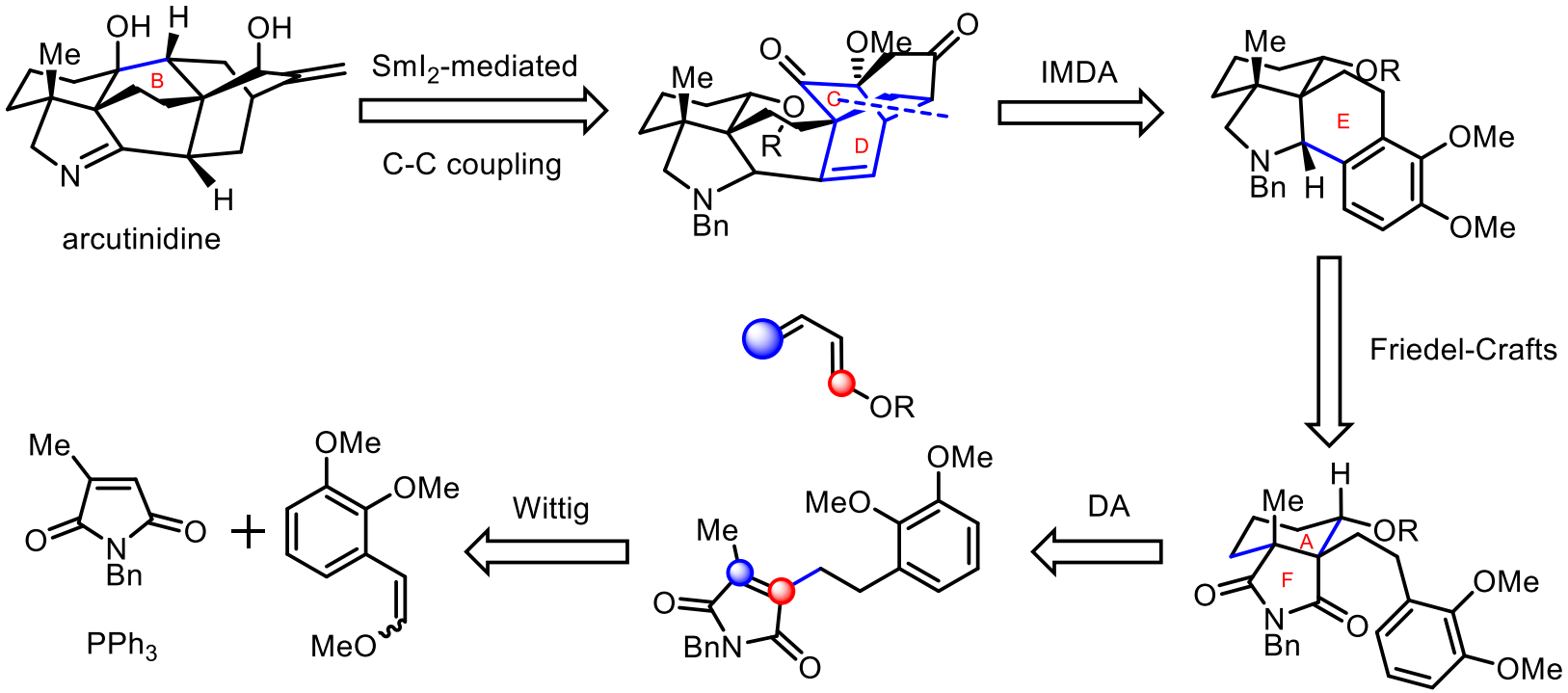
Asymmetric synthesis is realized in a similar way.

Nie, W.; Gong, J.; Chen, Z.-H.; Liu, J.-Z.; Tian, D.; Song, H.; Liu, X.-Y.; Qin, Y. *J. Am. Chem. Soc*. **2019**, *141*, 9712.

III Total Synthesis of Arcutines (by Sarpong)

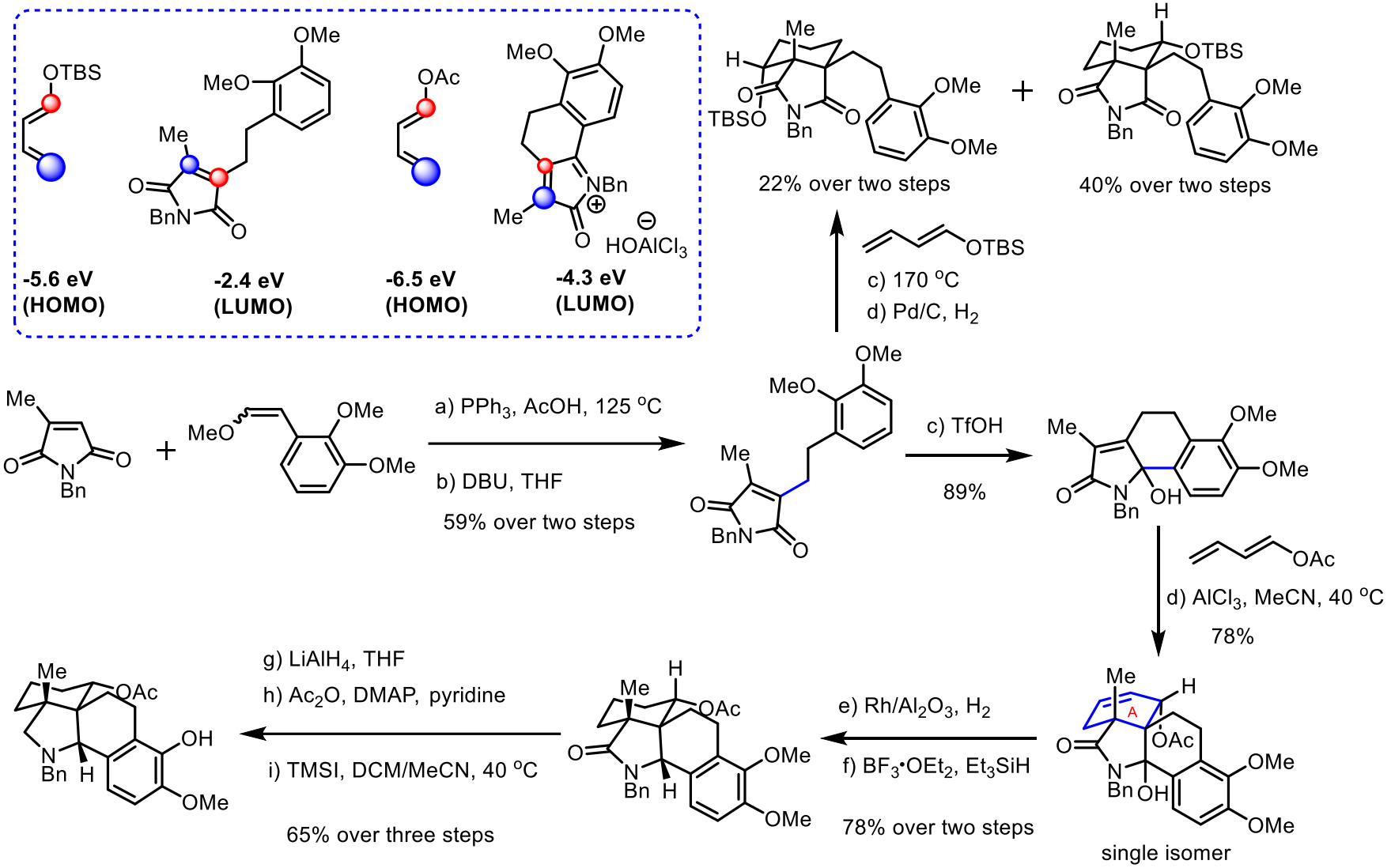
Sarpong finished the total synthesis of arcutinidine almost at the same time.

Sarpong's design:



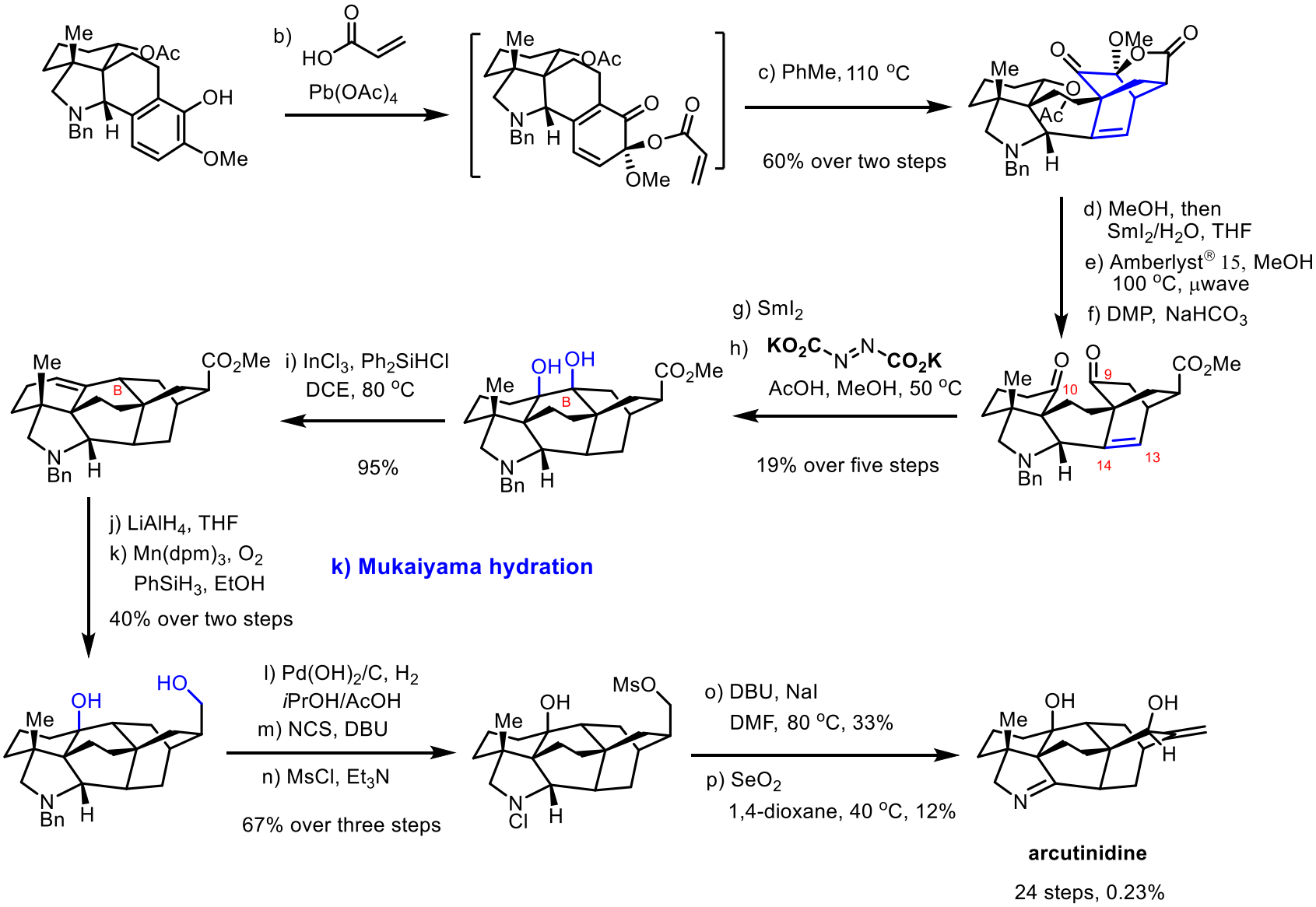
Owens, K. R.; McCowen, S. V.; Blackford, K. A.; Ueno, S. Hirooka, Y.; Weber, M. Sarpong, R. *J. Am. Chem. Soc*. **2019**, *141*, 13713.

III Total Synthesis of Arcutines (by Sarpong)



Owens, K. R.; McCowen, S. V.; Blackford, K. A.; Ueno, S. Hirooka, Y.; Weber, M. Sarpong, R. *J. Am. Chem. Soc*. **2019**, *141*, 13713.

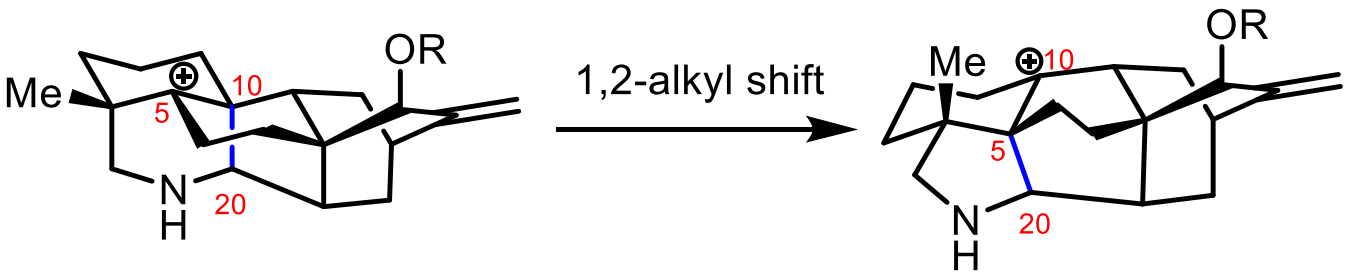
III Total Synthesis of Arcutines (by Sarpong)



Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem*. **2001**, *66*, 7741
Isayama, S.; Mukaiyama, T. *Chem. Lett*. **1989**, 1071.

III Total Synthesis of Arcutines (by Li)

What can we learn from the biosynthesis?



(hetidine type)

(arcutine type)

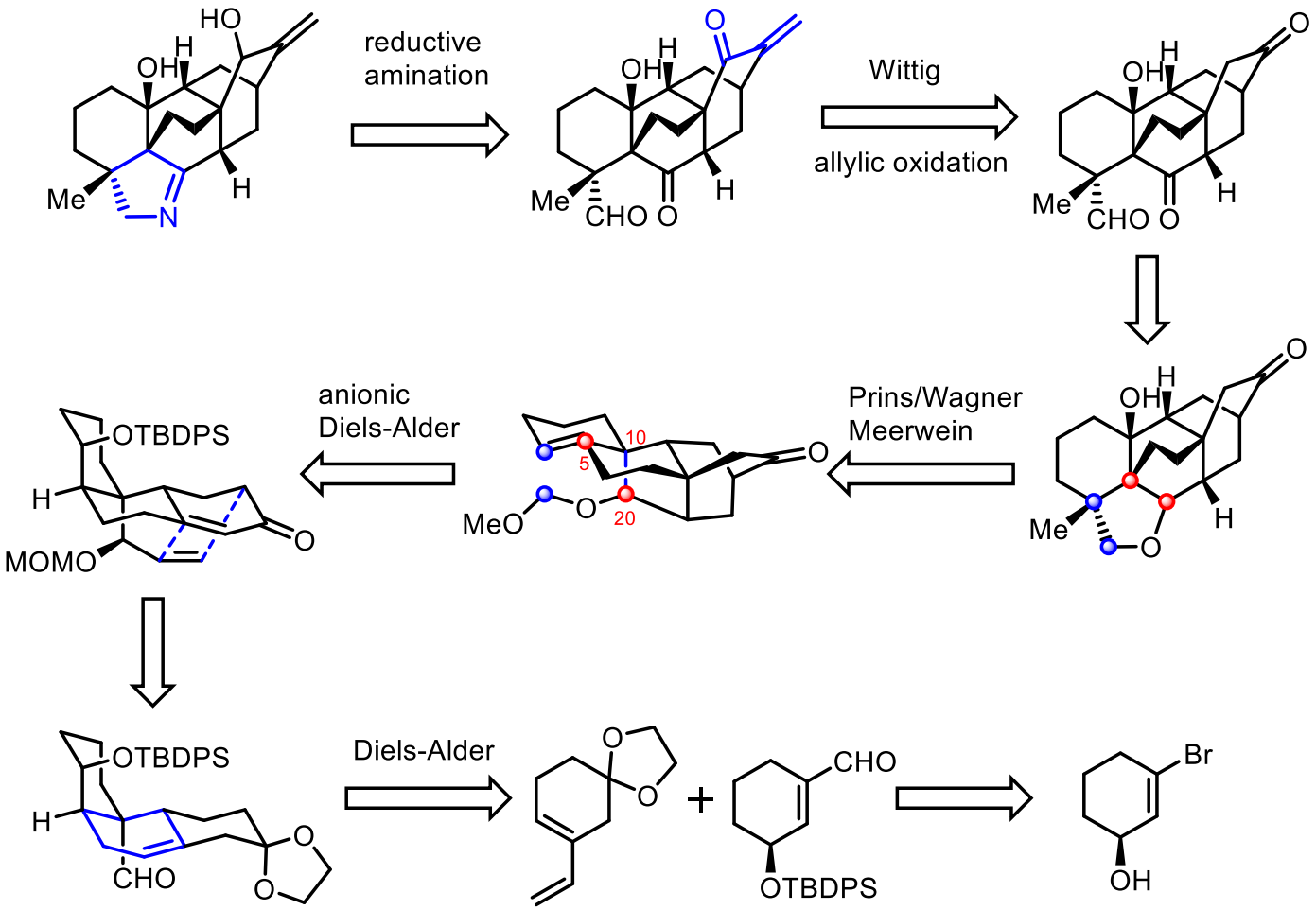
Challenges: how to install a cabocation at the C5 position;

how to install a six-member heterocycle to promote 1,2-alkyl shift.

Weber, M.; Owens, K.; Sarpong, R. *Tetrahedron Lett.* **2015**, *56*, 3600.

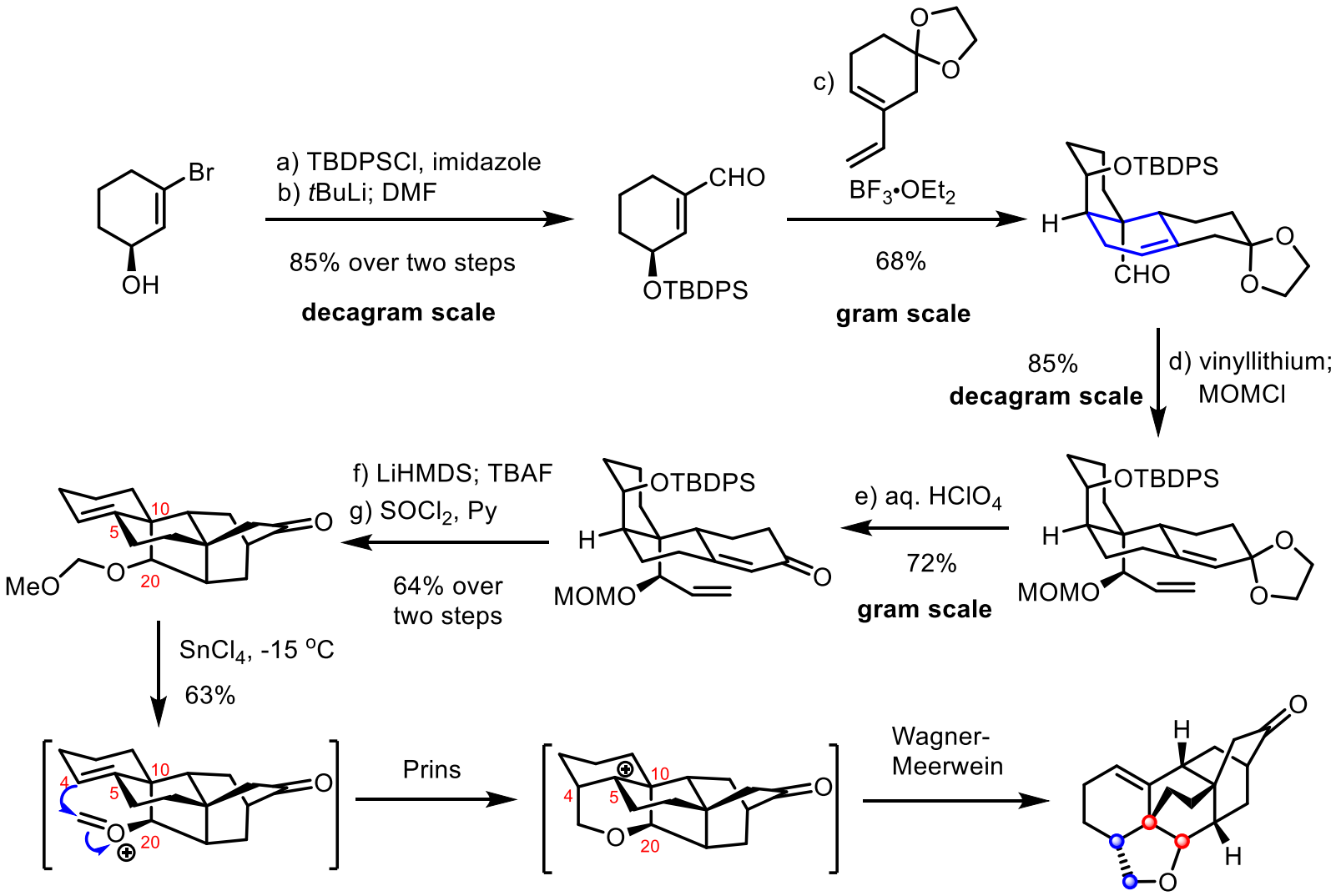
III Total Synthesis of Arcutines (by Li)

Li's design:



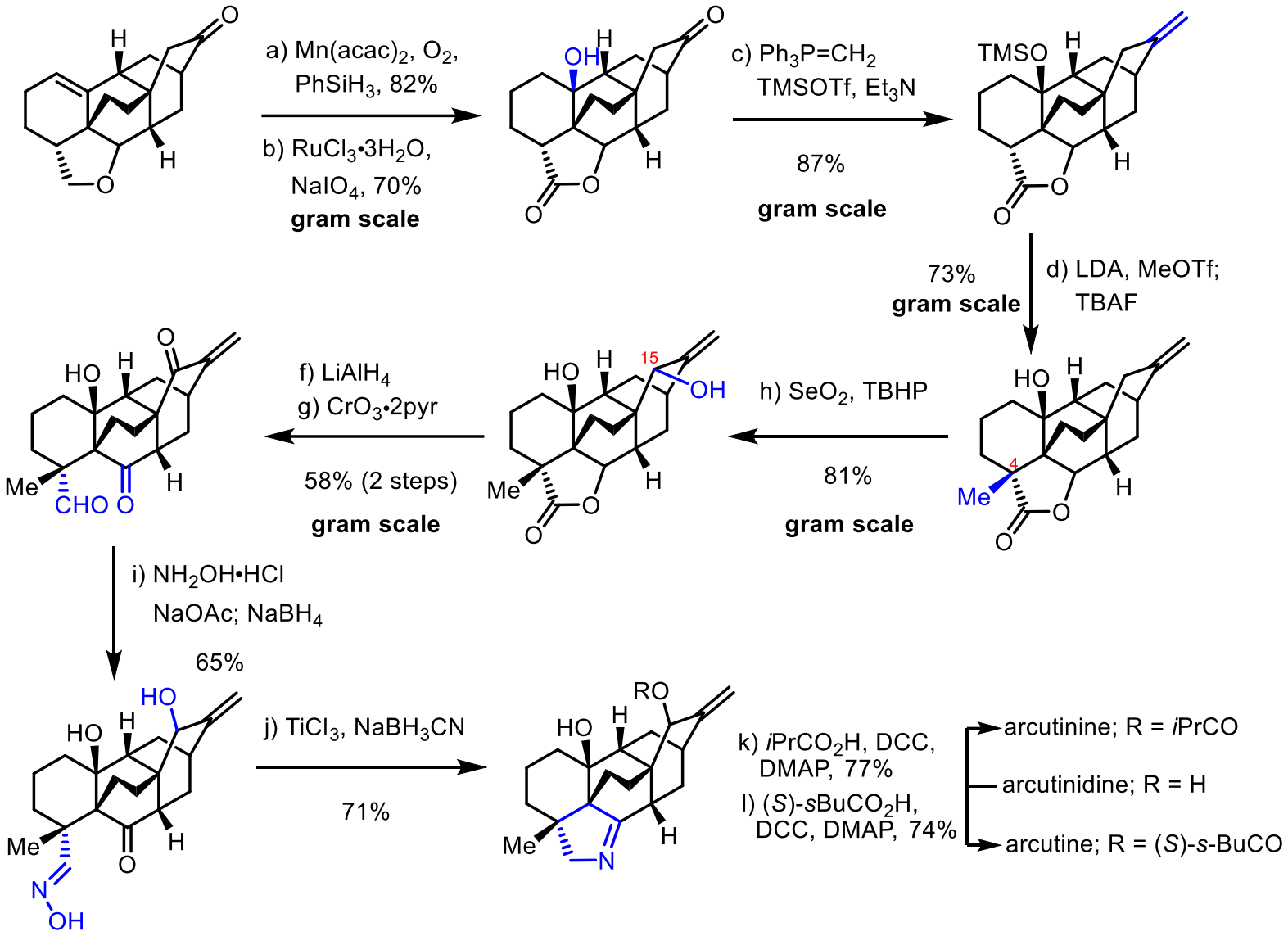
Zhou, S.-P.; Xia, K.-F.; Leng, X.-B.; Li, A. *J. Am. Chem. Soc.* **2019**, *141*, 13718.

III Total Synthesis of Arcutines (by Li)



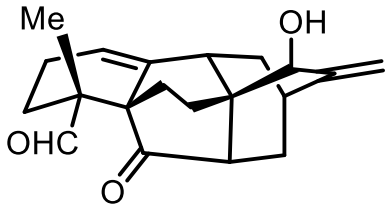
Zhou, S.-P.; Xia, K.-F.; Leng, X.-B.; Li, A. *J. Am. Chem. Soc.* **2019**, *141*, 13718.

III Total Synthesis of Arcutines (by Li)



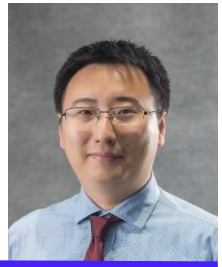
Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem*. **1981**, *46*, 3936.
Leeds, J. P.; Kirst, H. A. *Synth. Commun*. **1988**, *18*, 777.

Contents



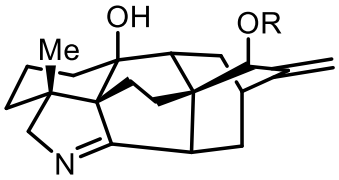
Atropurpuran

Qin, Y. [2016; 25 steps, 0.41%]
First total synthesis; racemic
Key steps: oxidative dearomatization(RDOD)/IMDA cascade;
SmI_2-mediated C-C coupling.



Xu, J. [2019; 13 steps, 0.70%]
Avoiding protective groups; racemic
Key steps: RCEM-RDOD/IMDA to build the core skeleton.

Qin, Y. [2019; for: (±)arcutinine: 17 steps, 1.23%]
First total synthesis; racemic and asymmetric
Key steps: similar to the synthesis of atropurpuran;
aza-Wacker to build the pyrroline motif.



Arcutine; R=(*S*)-*s*-BuCO
Arcutinine; R=*i*-PrO
Arcutinidine; R=H

Sarpong, R. [2019; (±)arcutinine: 24 steps, 0.23%]
Almost simultaneously with Qin, Y.; racemic
Key steps: Wittig reaction;
Friedel-Crafts cyclization;
Diels-Alder reaction;

Li, A. [2019; for (−)arcutinine: 18 steps, 0.86%]
Imitate biosynthesis; asymmetric.
Key steps: Prins/Wagner-Meerwein;
reductive amination.

.

Thanks for your kind attention!