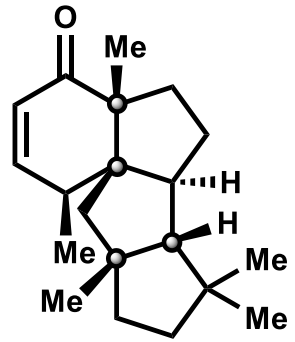
Total Synthesis of Conidiogenone B



Conidiogenone B

Reporter: Shenghan Cai

Supervisor: Prof. Quan Cai

2026.05.08

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  - Yongqiang Tu (2016)
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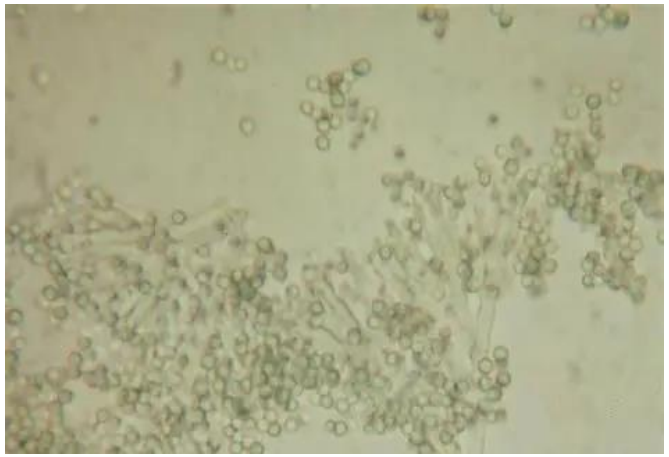
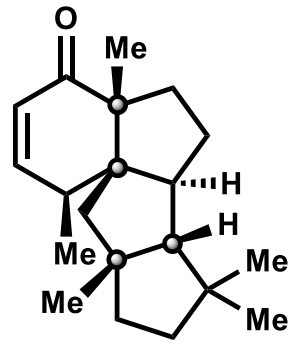
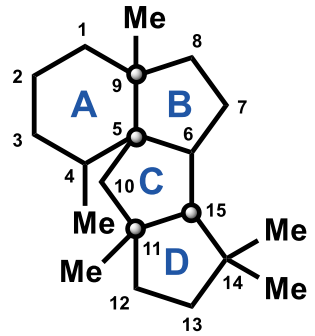
Conidiogenone B



Penicillium cyclopium



Conidiogenone B



6/5/5/5 (A/B/C/D) tetracyclic carbon framework

- Conidiogenone B: Potent antibacterial activity, MICs (μg/mL):
  MRSA (8), *S. epidermidis* (8)
  P. aeruginosa (8), *P. fluorescens* (8)

- Conidiogenone B-G: Potent anticancer activity (IC_{50}: low μM to nM)

Structure features

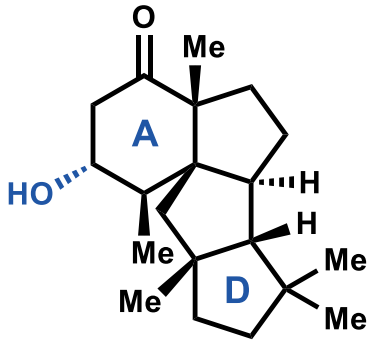
- 6/5/5/5-fused rings
- 4 all-carbon quaternary centers
- 6 stereocenters

Bioactivity

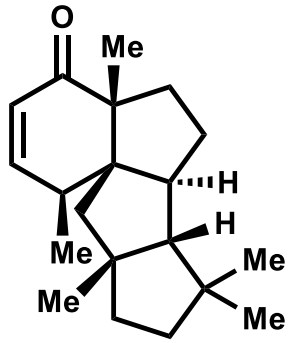
- Induction of conidiogenesis
- Anti-inflammatory activity
- Antibacterial activity
- Anticancer activity

Roncal, T.; Cordobés, S.; Sterner, O.; Ugalde, U. *Eukaryot. Cell* **2002**, *1*, 823−829.; Du, L.; Li, D.; Zhu, T.; Cai, S.; Wang, F.; Xiao, X.; Gu, Q. *Tetrahedron* **2009**, *65*, 1033−1039.; Gao, S.-S.; Li, X.-M.; Zhang, Y.; Li, C.-S.; Wang, B.-G. *Chem. Biodiversity* **2011**, *8*, 1748−1753.

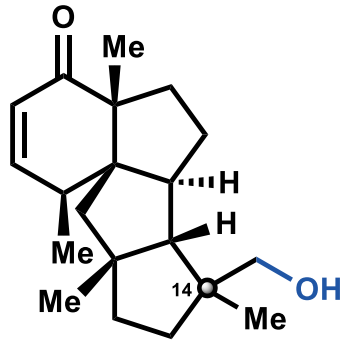
Structures of Conidiogenones and Conidiogenol



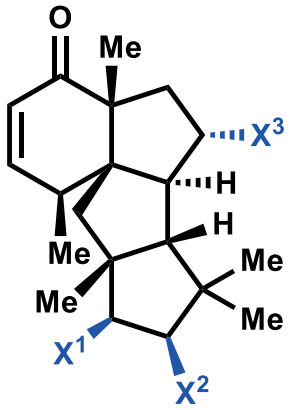
Conidiogenone (**1**)



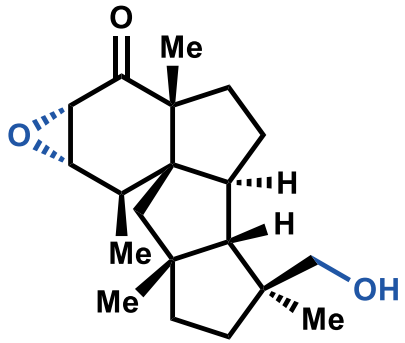
Conidiogenone B (**2**)



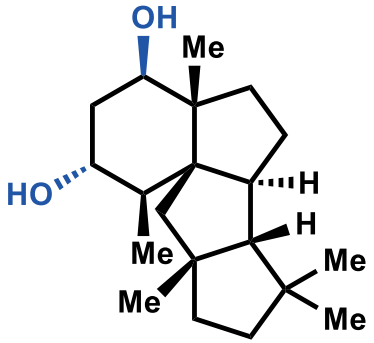
Conidiogenone C (14*S*, **3**)
Conidiogenone D (14*R*, **4**)



Conidiogenone E (X^1 = OH, **5**)
Conidiogenone F (X^2 = OH, **6**)
Conidiogenone G (X^3 = OH, **7**)



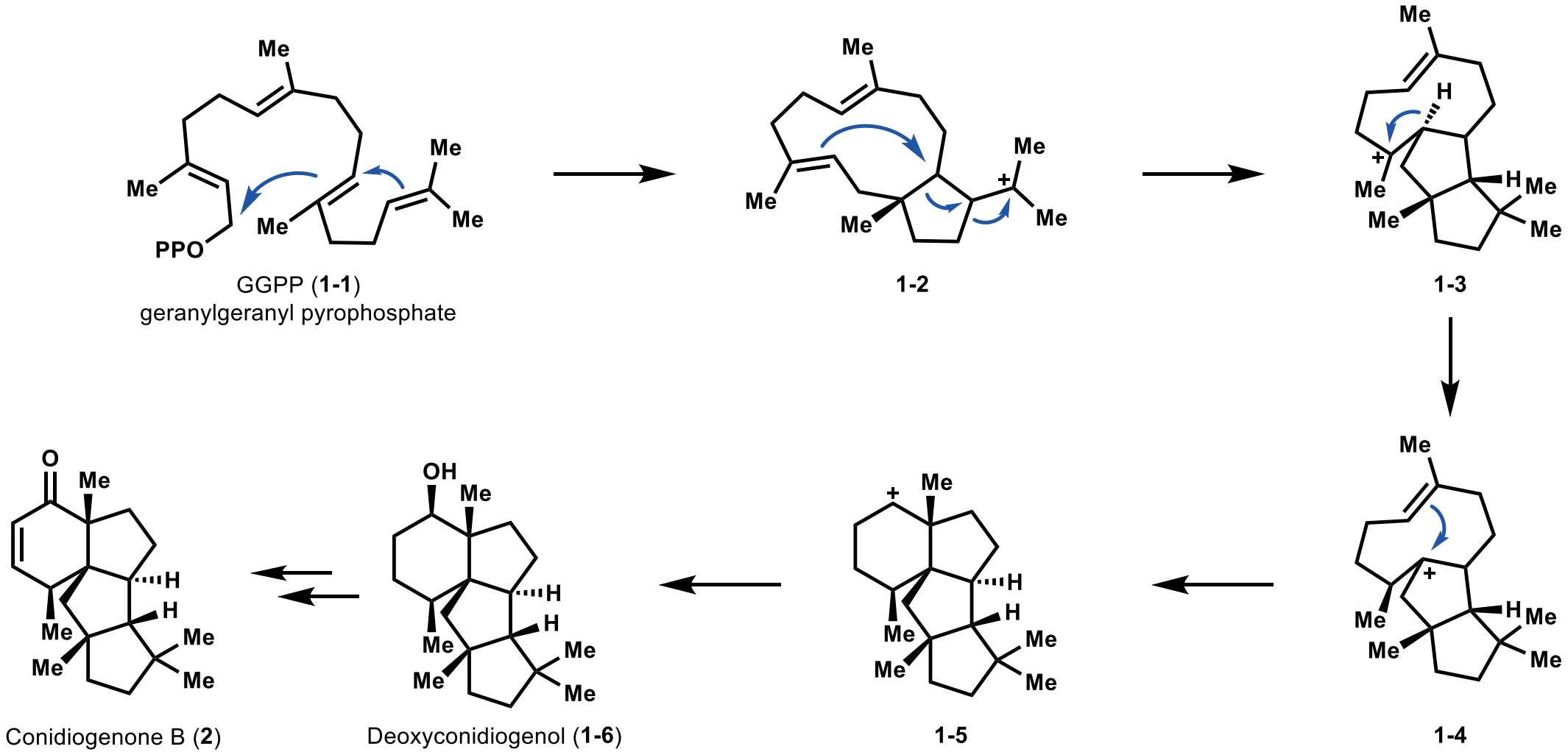
Conidiogenone K (**8**)



Conidiogenol (**9**)

Roncal, T.; Cordobés, S.; Sterner, O.; Ugalde, U. *Eukaryot. Cell* **2002**, *1*, 823−829.; Du, L.; Li, D.; Zhu, T.; Cai, S.; Wang, F.; Xiao, X.; Gu, Q. *Tetrahedron* **2009**, *65*, 1033−1039.

Biosynthesis of Conidiogenone B



Shiina, T.; Nakagawa, K.; Fujisaki, Y.; Ozaki, T.; Liu, C.; Toyomasu, T.; Hashimoto, M.; Koshino, H.; Minami, A.; Kawaide, H.; Oikawa, H. *Biosci. Biotechnol. Biochem.* **2019**, *83*, 192−201.

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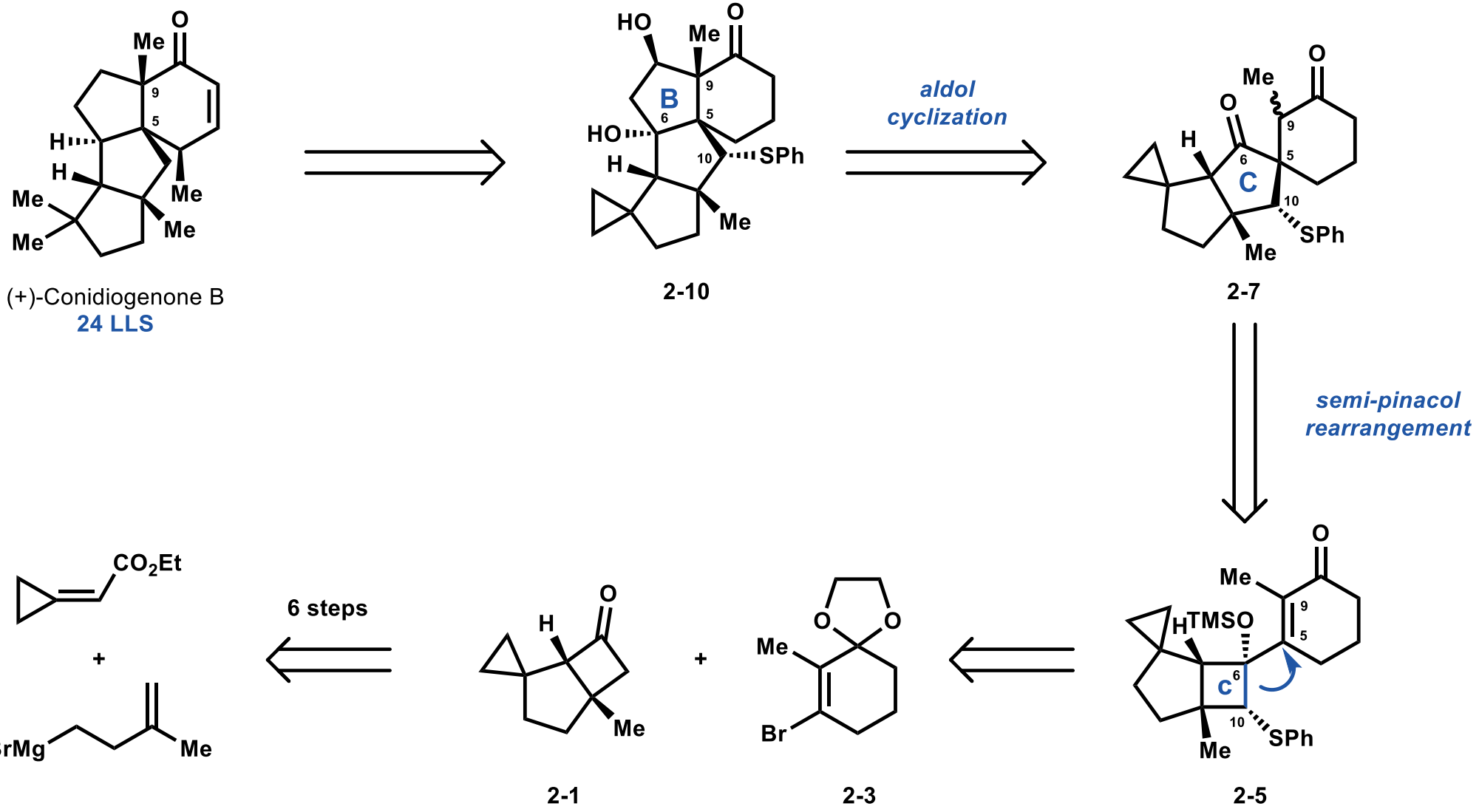
➢ Summary

Total Synthesis of (+)-Conidiogenone B — *Tu* (2016)

Retrosynthetic Analysis



Hou, S.-H.; Tu, Y.-Q.; Wang, S.-H.; Xi, C.-C.; Zhang, F.-M.; Wang, S.-H.; Li, Y.-T.; Liu, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 4456−4460.

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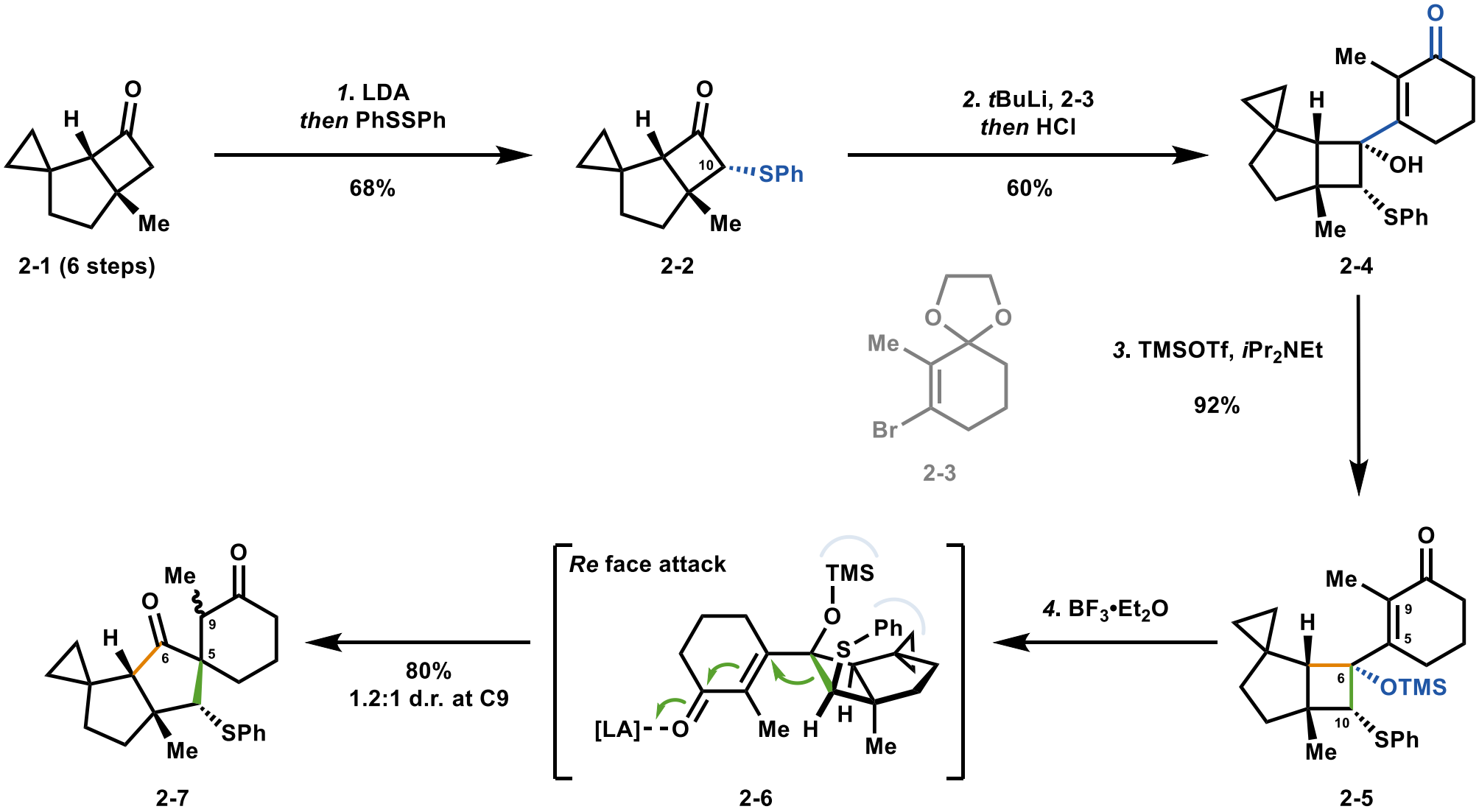

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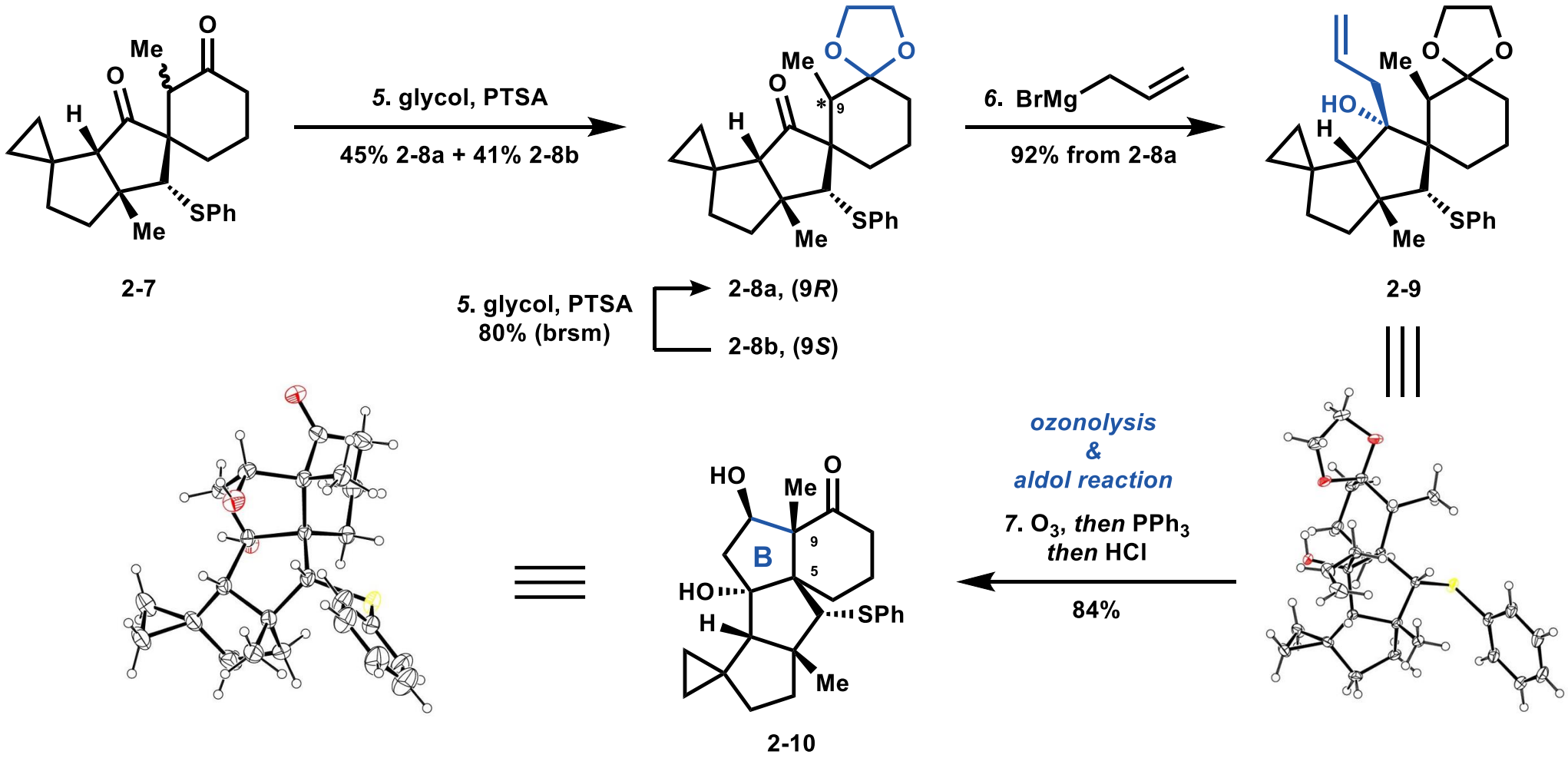

Hou, S.-H.; Tu, Y.-Q.; Wang, S.-H.; Xi, C.-C.; Zhang, F.-M.; Wang, S.-H.; Li, Y.-T.; Liu, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 4456−4460.

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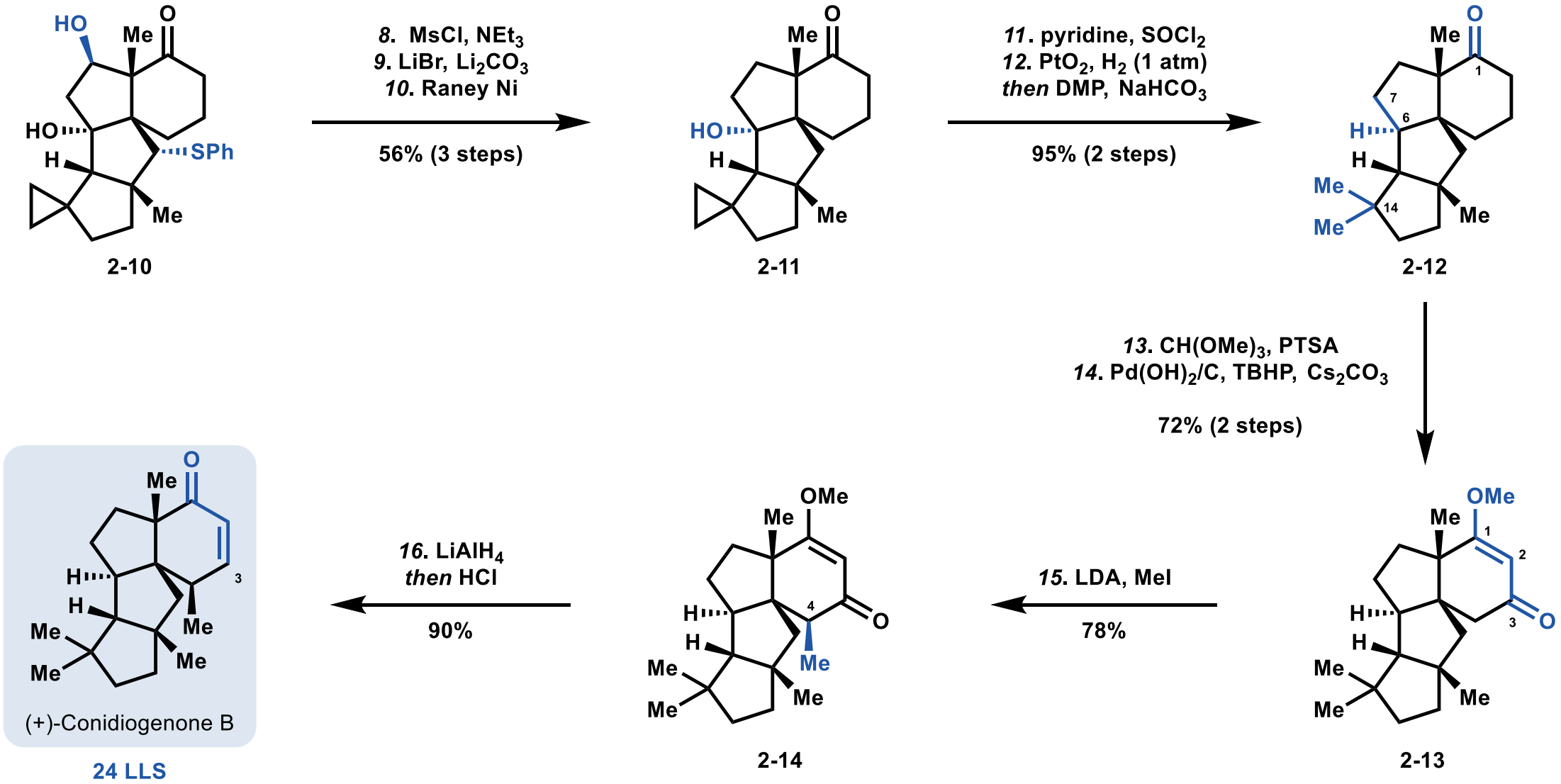
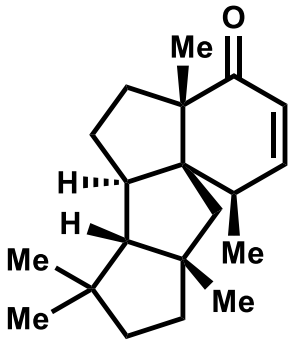


Hou, S.-H.; Tu, Y.-Q.; Wang, S.-H.; Xi, C.-C.; Zhang, F.-M.; Wang, S.-H.; Li, Y.-T.; Liu, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 4456−4460.

Total Synthesis of (+)-Conidiogenone B — *Tu* (2016)

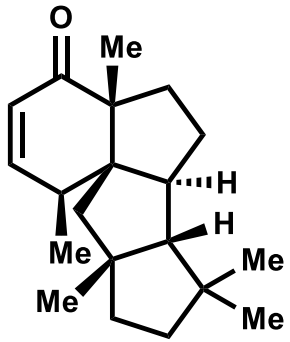
Optical rotation of
(+)-Conidiogenone B (*ent*-**2**)
$[\alpha]_D^{23.3}$ = +16.1 (*c* = 0.62 in MeOH)
$[\alpha]_D^{23.3}$ = +7.9 (*c* = 0.76 in $CHCl_3$)

CD spectrum of
(+)-Conidiogenone B (*ent*-**2**) (MeOH)
λ_{max} ($\Delta\varepsilon$) = 230 (-16.9), 240 (-19.1), 308 (1.5), 348 nm (-5.1)



proposed absolute configuration of Conidiogenone B in original report

corrected by Tu



naturally occurring (−)-Conidiogenone B (**2**)

Optical rotation of
(−)-Conidiogenone B (**2**)
$[\alpha]_D^{20}$ = -6.0 (*c* = 0.55 in MeOH)

CD spectrum of
(−)-Conidiogenone B (**2**) (MeOH)
λ_{max} ($\Delta\varepsilon$) = 194 (-0.8), 234 (2.0), 305 (-0.2), 347 nm (0.6)

Li, D.; Zhu, T.; Cai, S.; Wang, F.; Xiao, X.; Gu, Q. *Tetrahedron* **2009**, *65*, 1033−1039.; Hou, S.-H.; Tu, Y.-Q.; Wang, S.-H.; Xi, C.-C.; Zhang, F.-M.; Wang, S.-H.; Li, Y.-T.; Liu, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 4456−4460.

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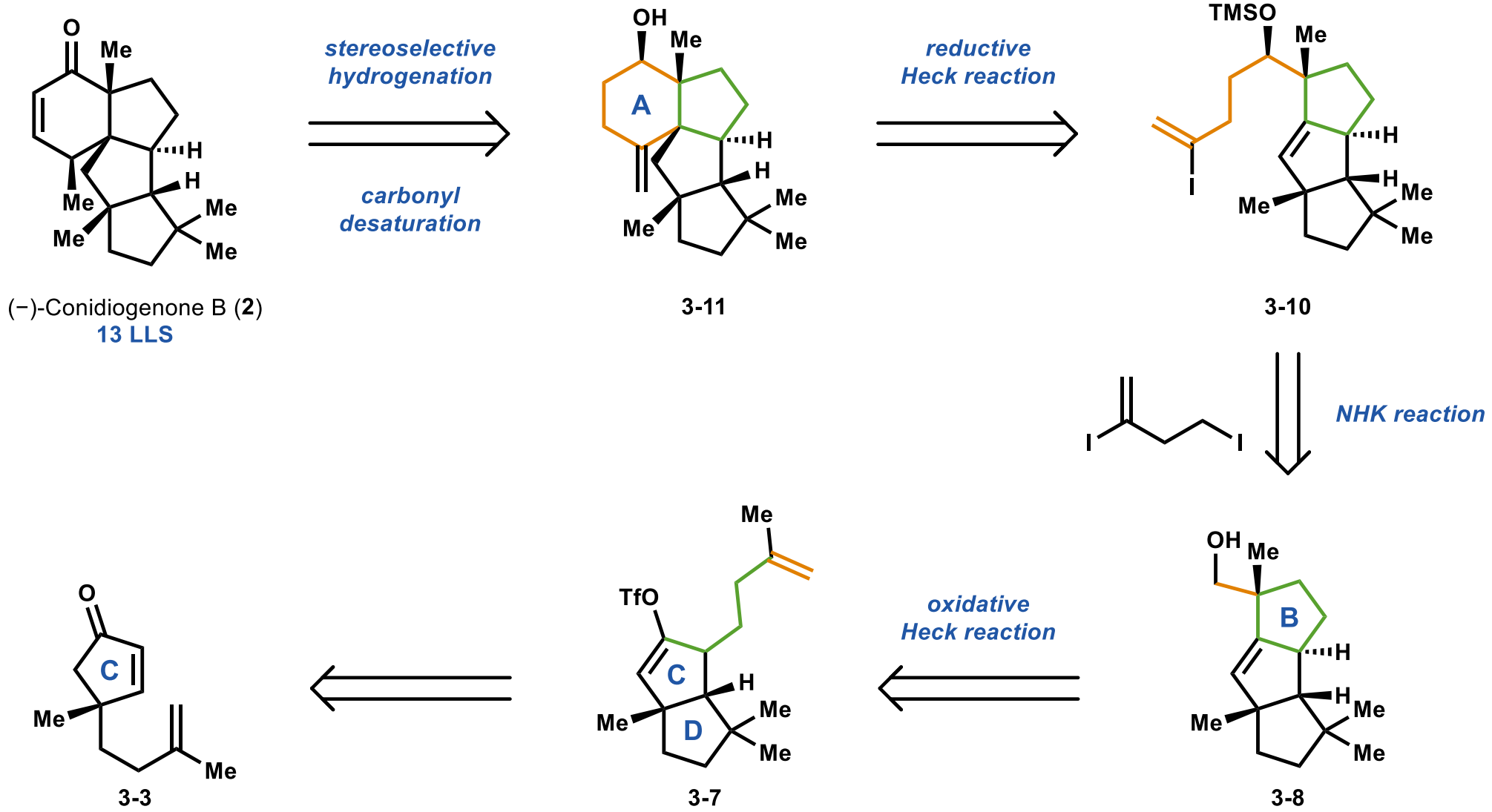
Total Synthesis of (−)-Conidiogenone B — *Snyder* (2019)

Retrosynthetic Analysis



(−)-Conidiogenone B (**2**)
13 LLS

3-11

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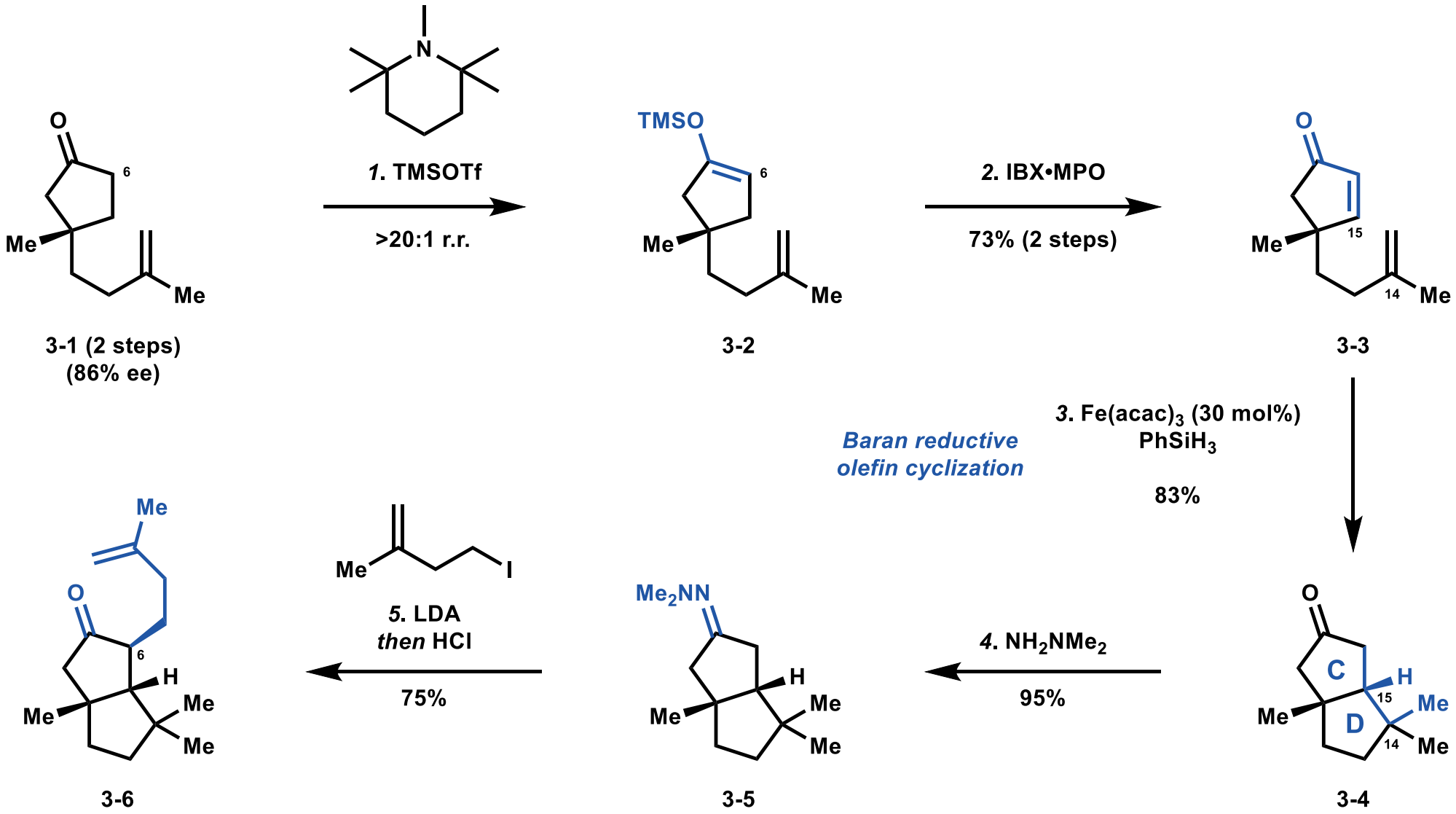
Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. *Nature* **2019**, *569*, 703−707.

Total Synthesis of (−)-Conidiogenone B — *Snyder* (2019)



Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. *Nature* **2019**, *569*, 703−707.

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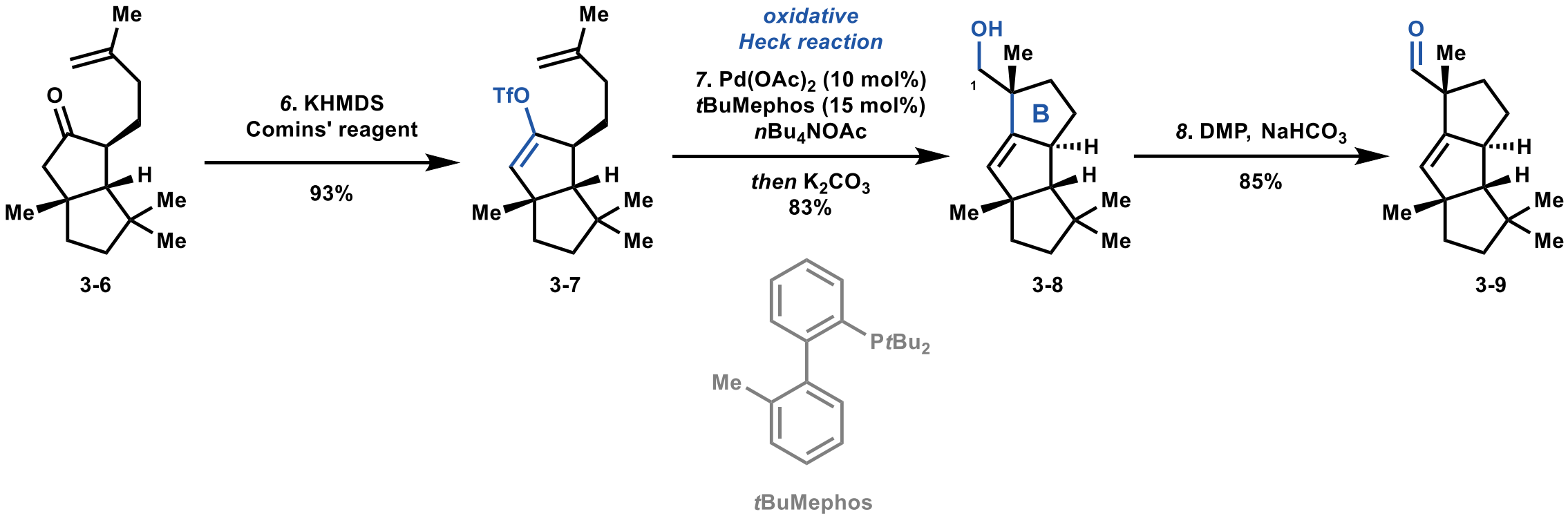

Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. *Nature* **2019**, *569*, 703−707.

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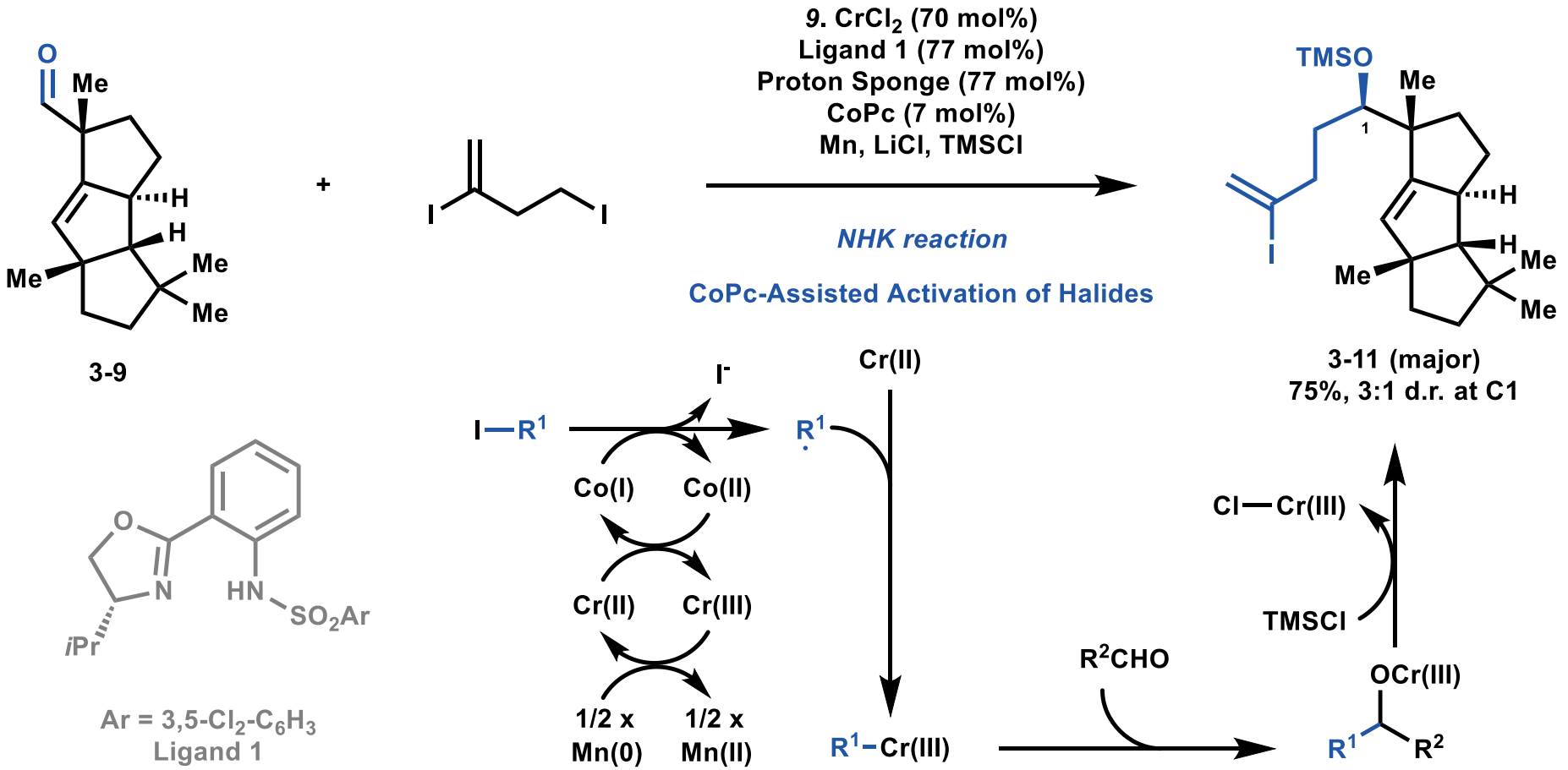
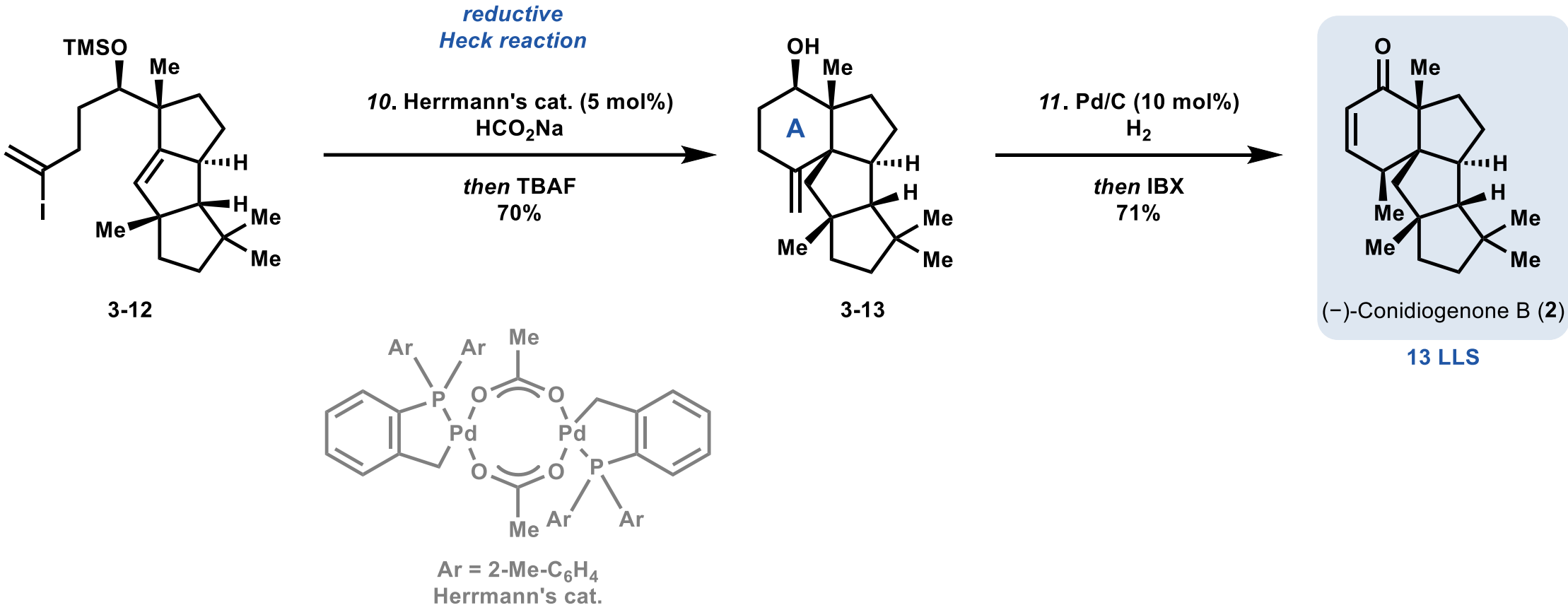


Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. *Nature* **2019**, *569*, 703−707.; Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387–15393.

Total Synthesis of (−)-Conidiogenone B — *Snyder* (2019)



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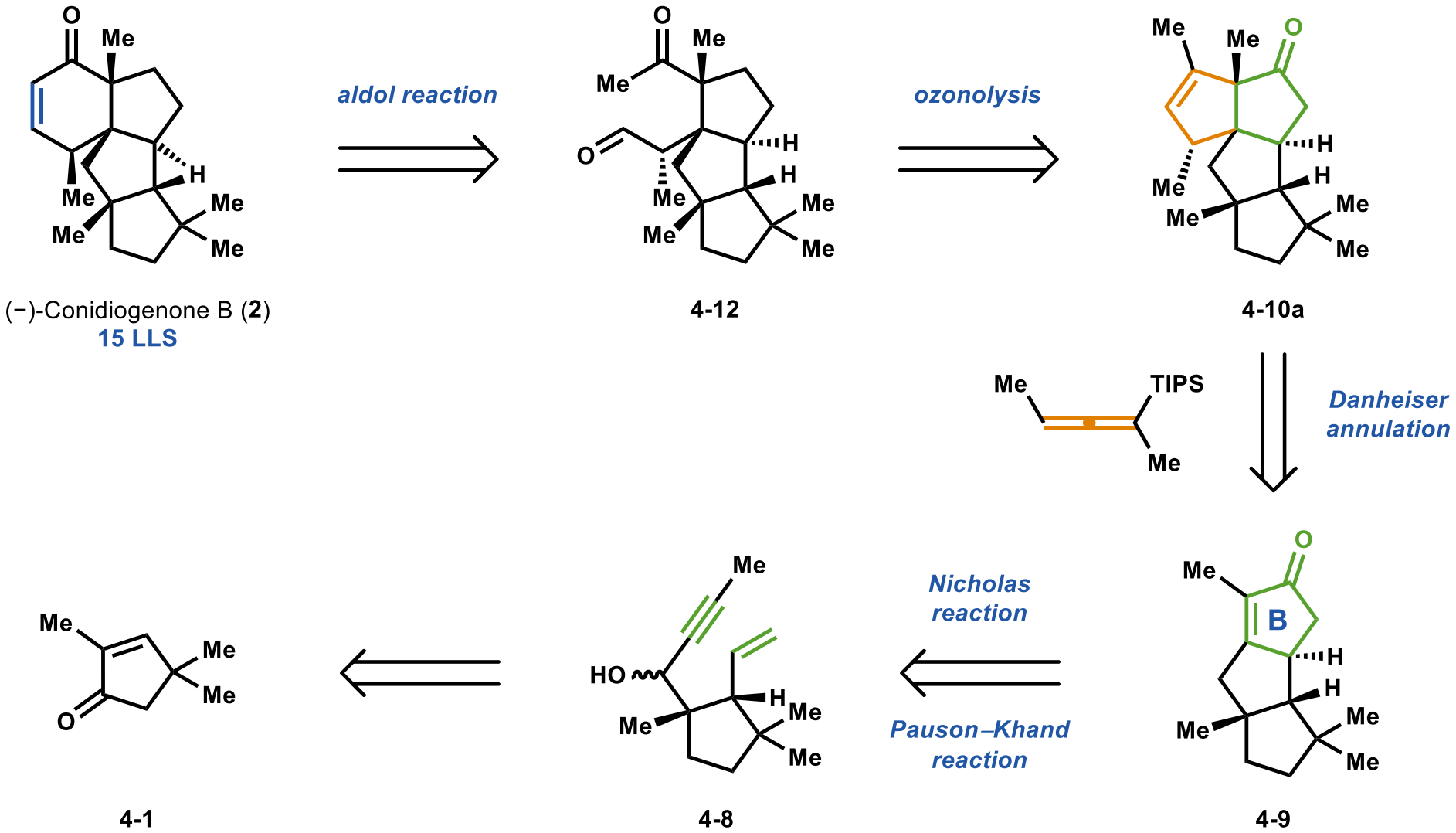
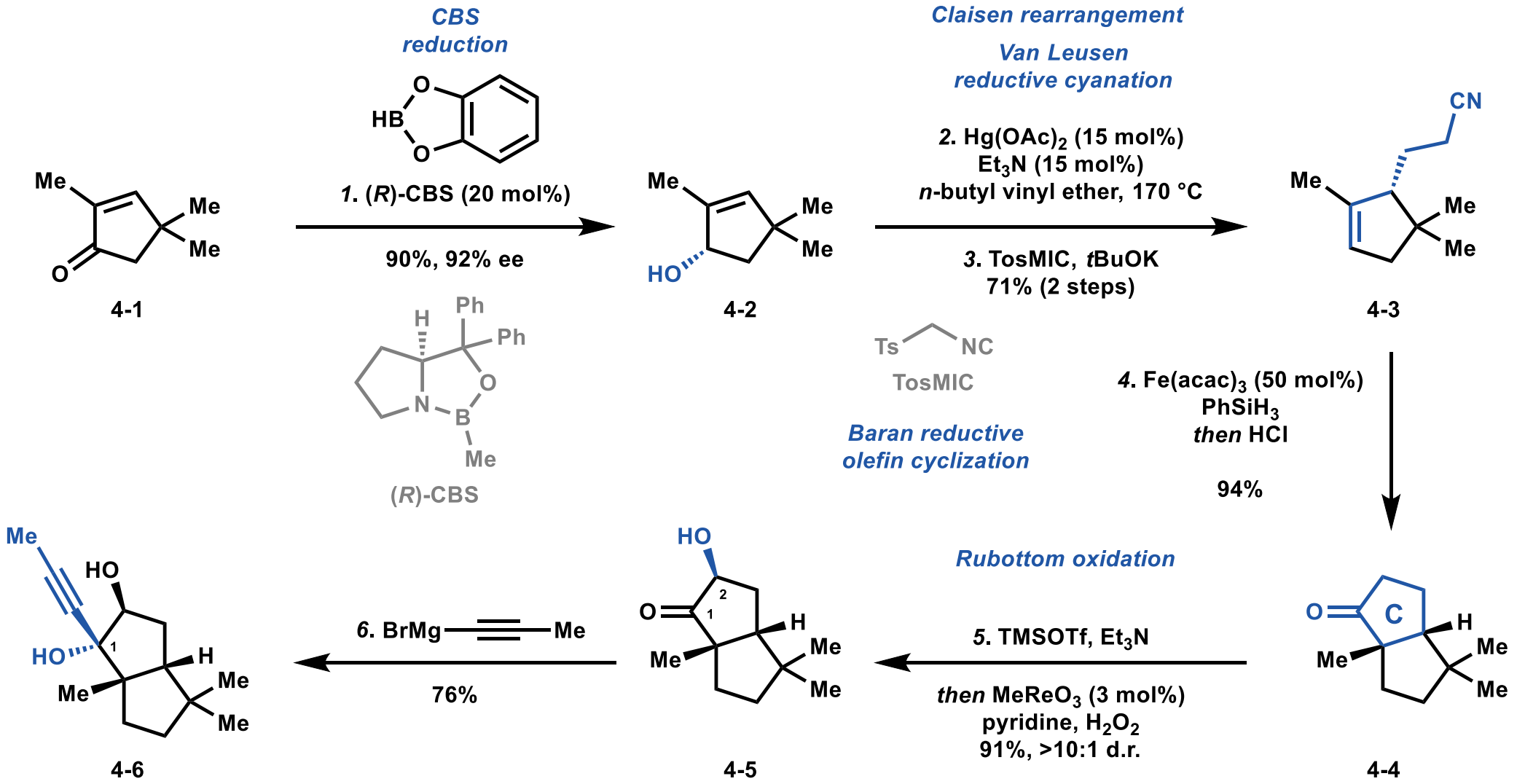


Xu, B.; Xun, W.; Su, S.; Zhai, H. *Angew. Chem., Int. Ed.* **2020**, *59*, 16475−16479.

Total Synthesis of (−)-Conidiogenone B — *Zhai* (2020)



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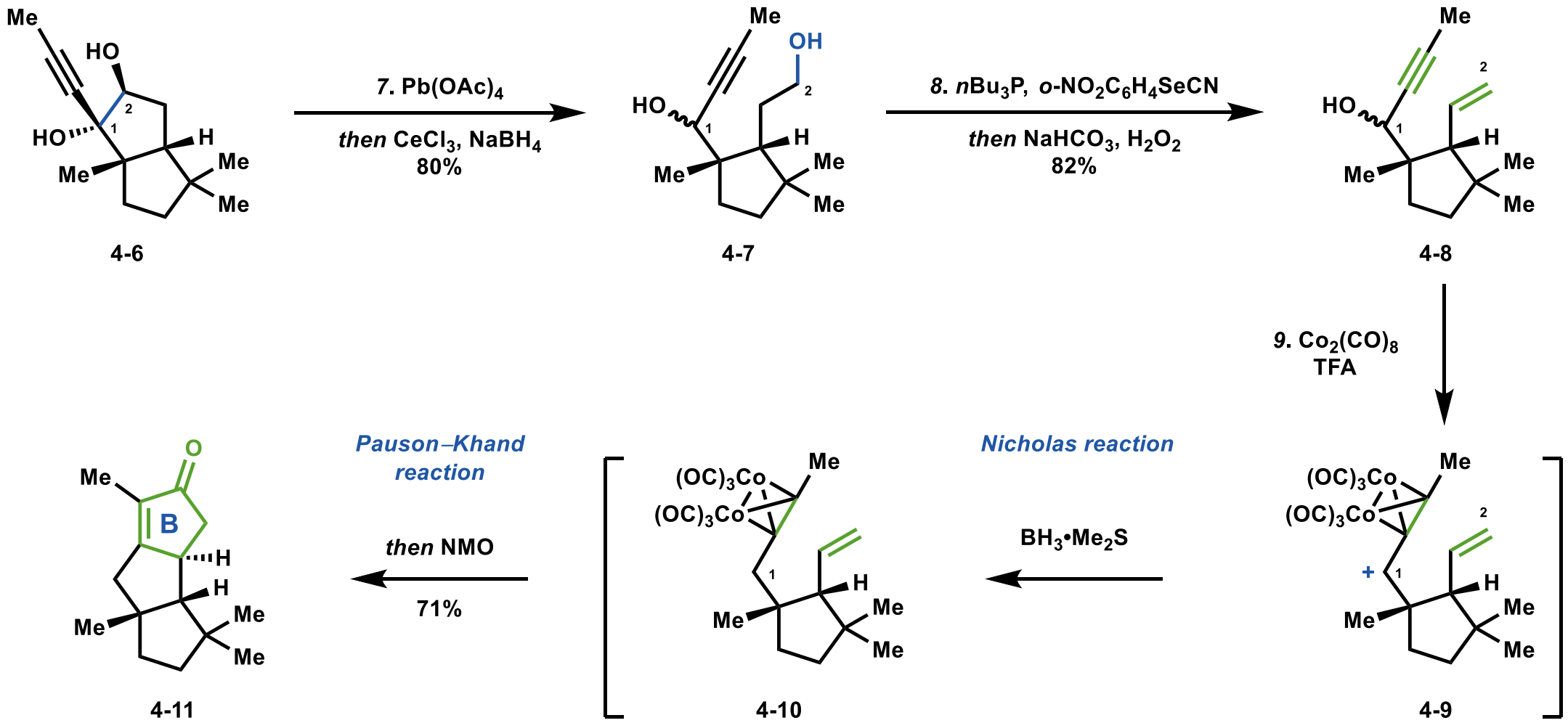

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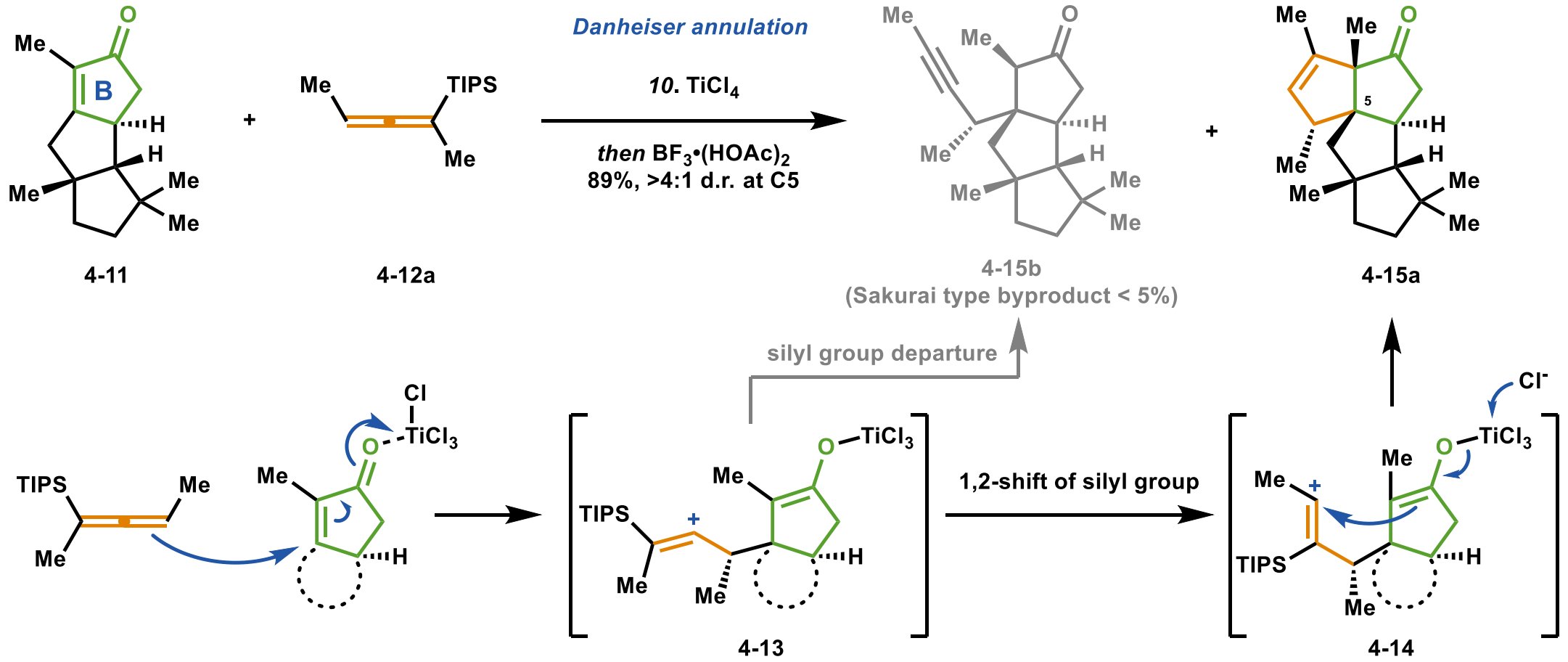

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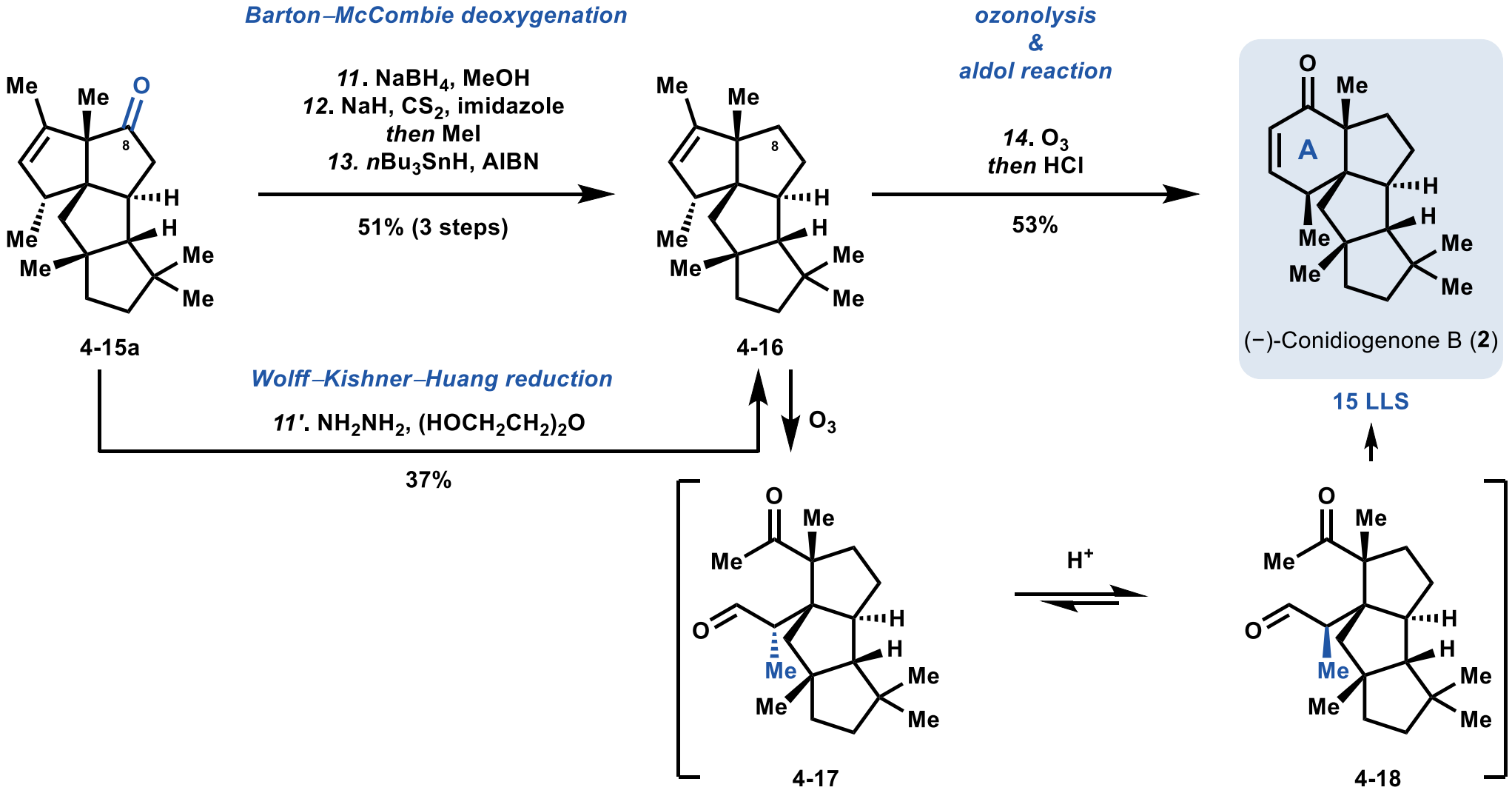

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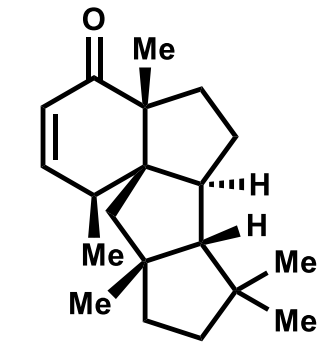
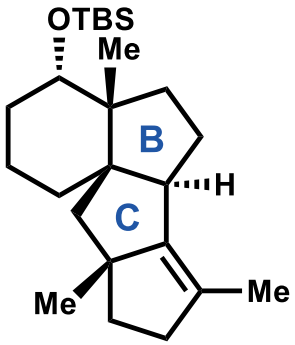


(−)-Conidiogenone B (**2**)
19 LLS
formal synthesis



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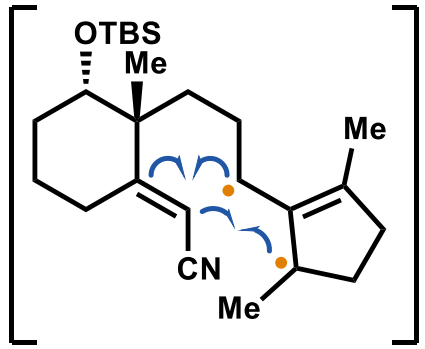

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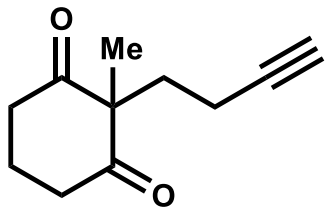

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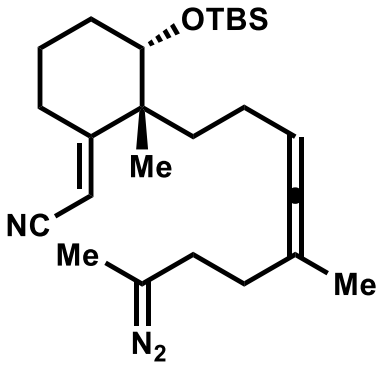

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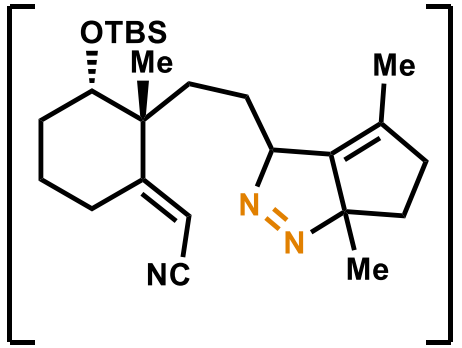
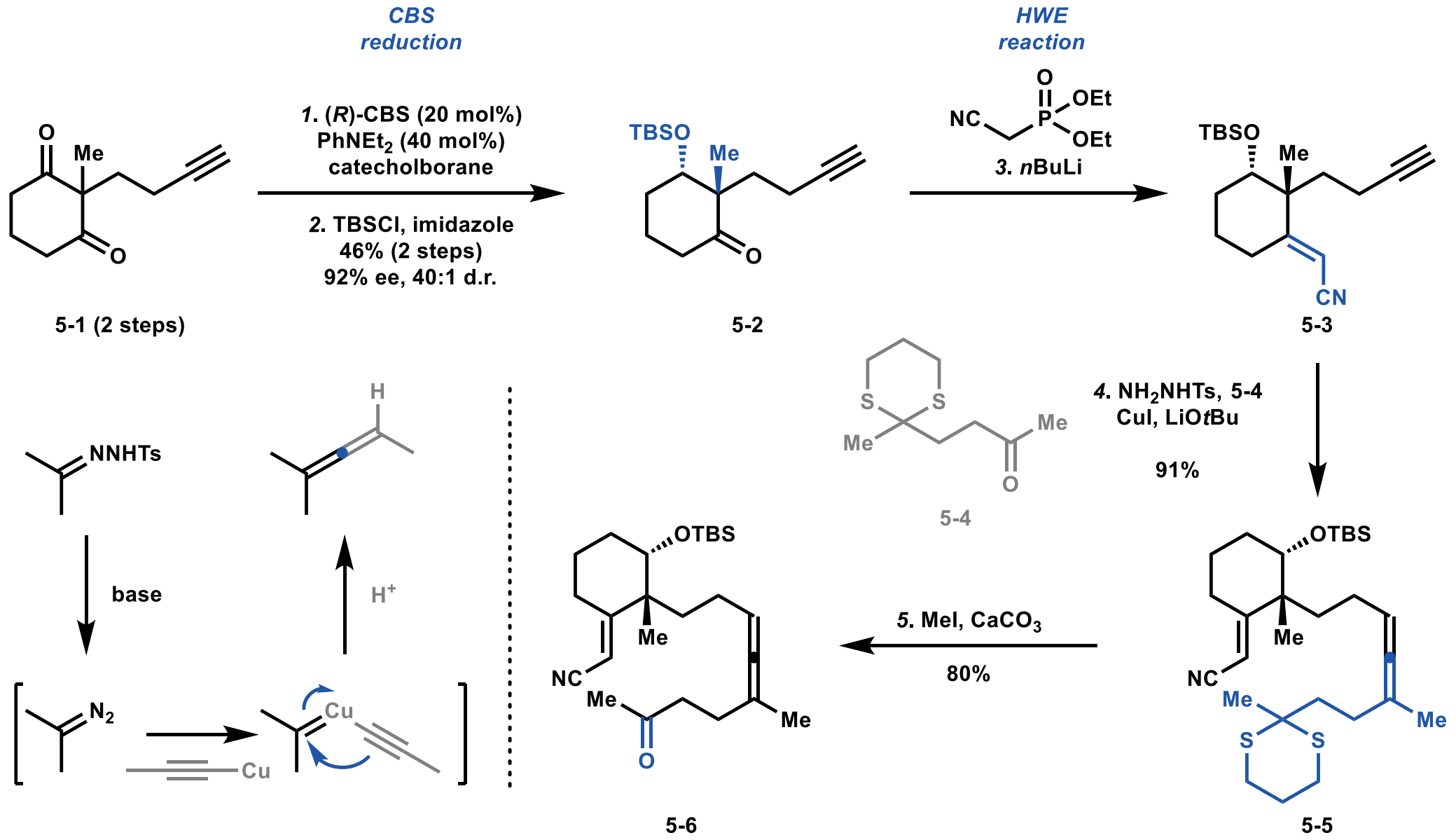


5-9

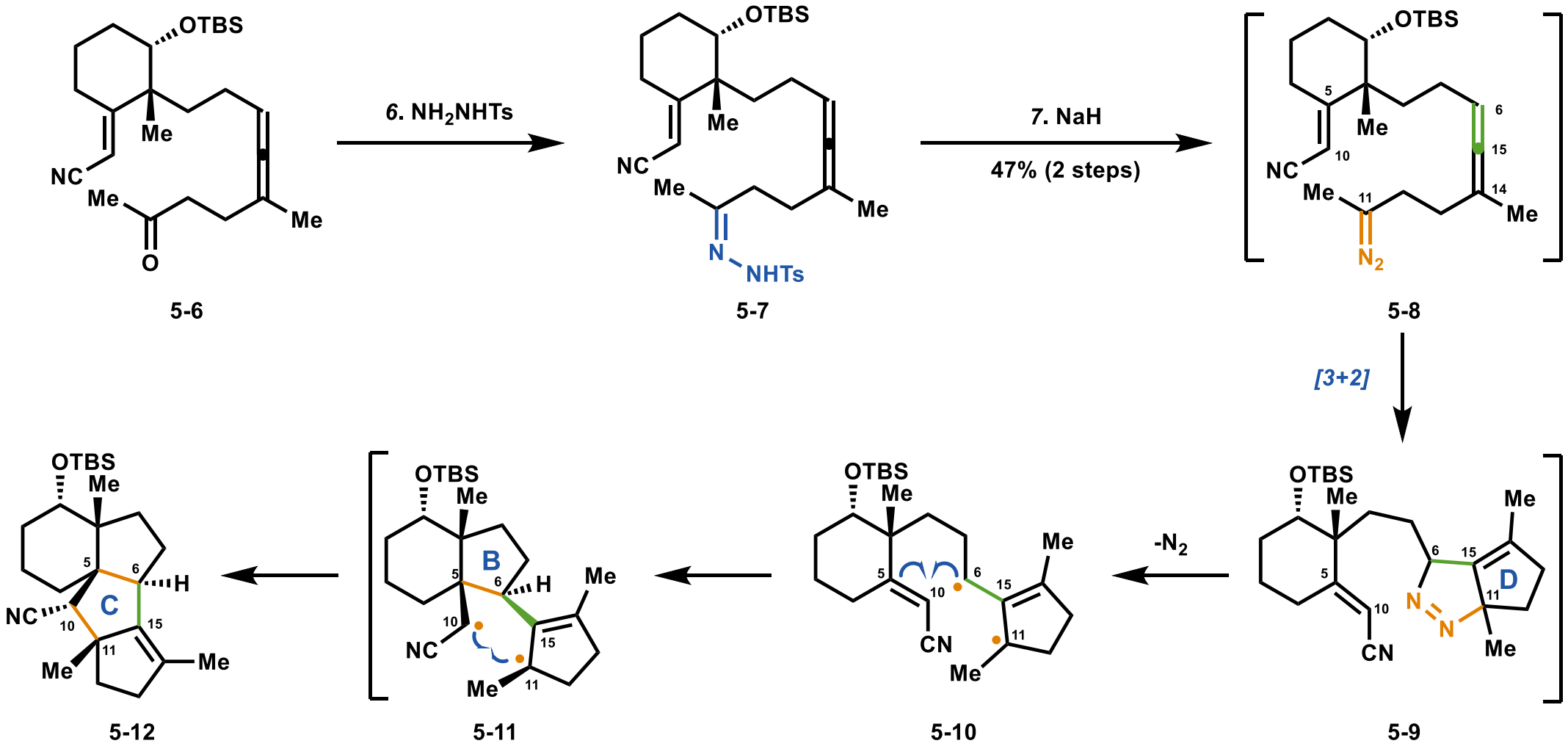
Kim, J.; Lee, S.; Han, S.; Lee, H.-Y. *Chem.* **2023**, *9*, 1270−1280.

Total Synthesis of (−)-Conidiogenone B — *Lee* & *Han* (2023)



Kim, J.; Lee, S.; Han, S.; Lee, H.-Y. *Chem.* **2023**, *9*, 1270−1280.; Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1236–1241.

Total Synthesis of (−)-Conidiogenone B — *Lee* & *Han* (2023)



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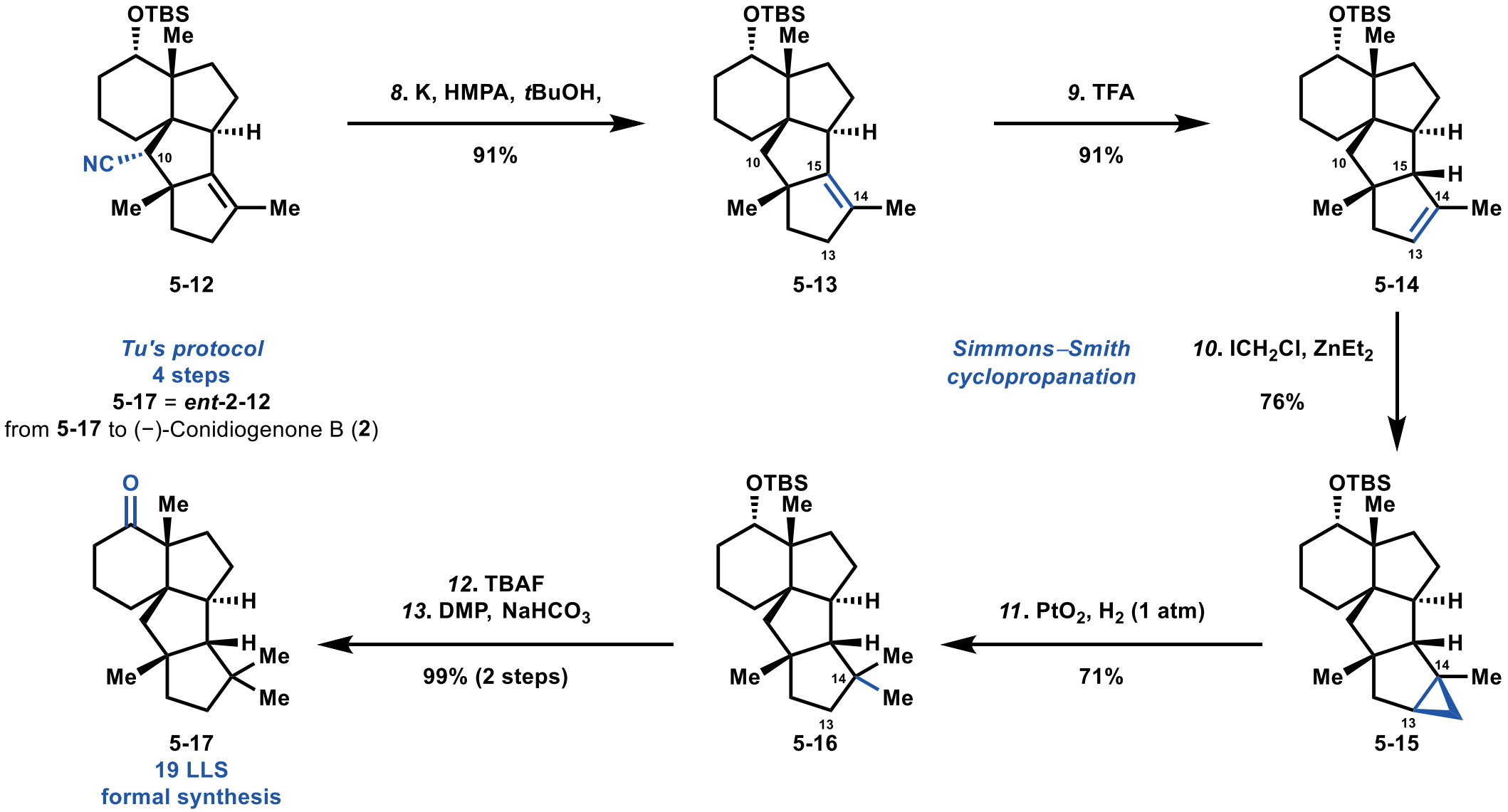

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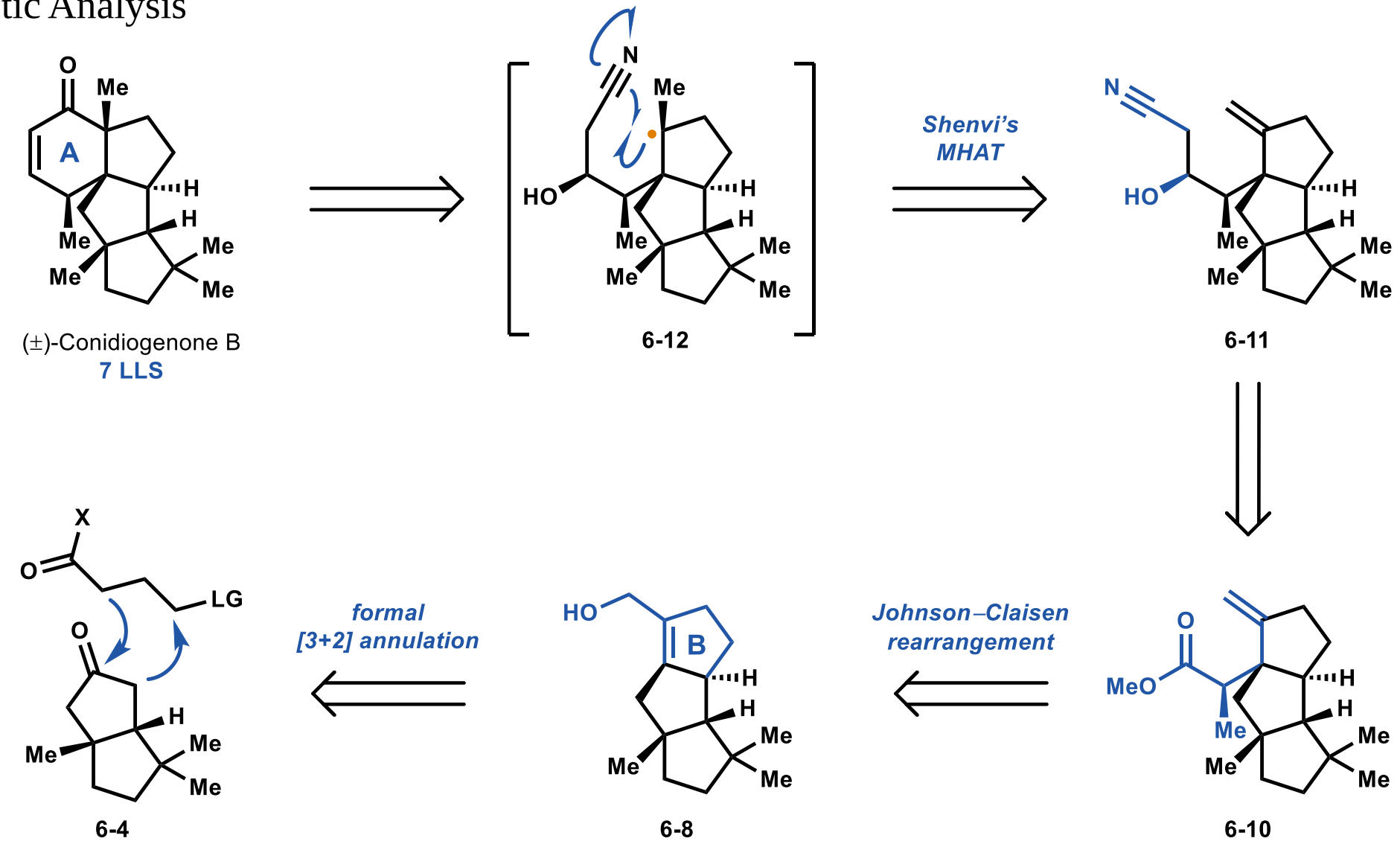
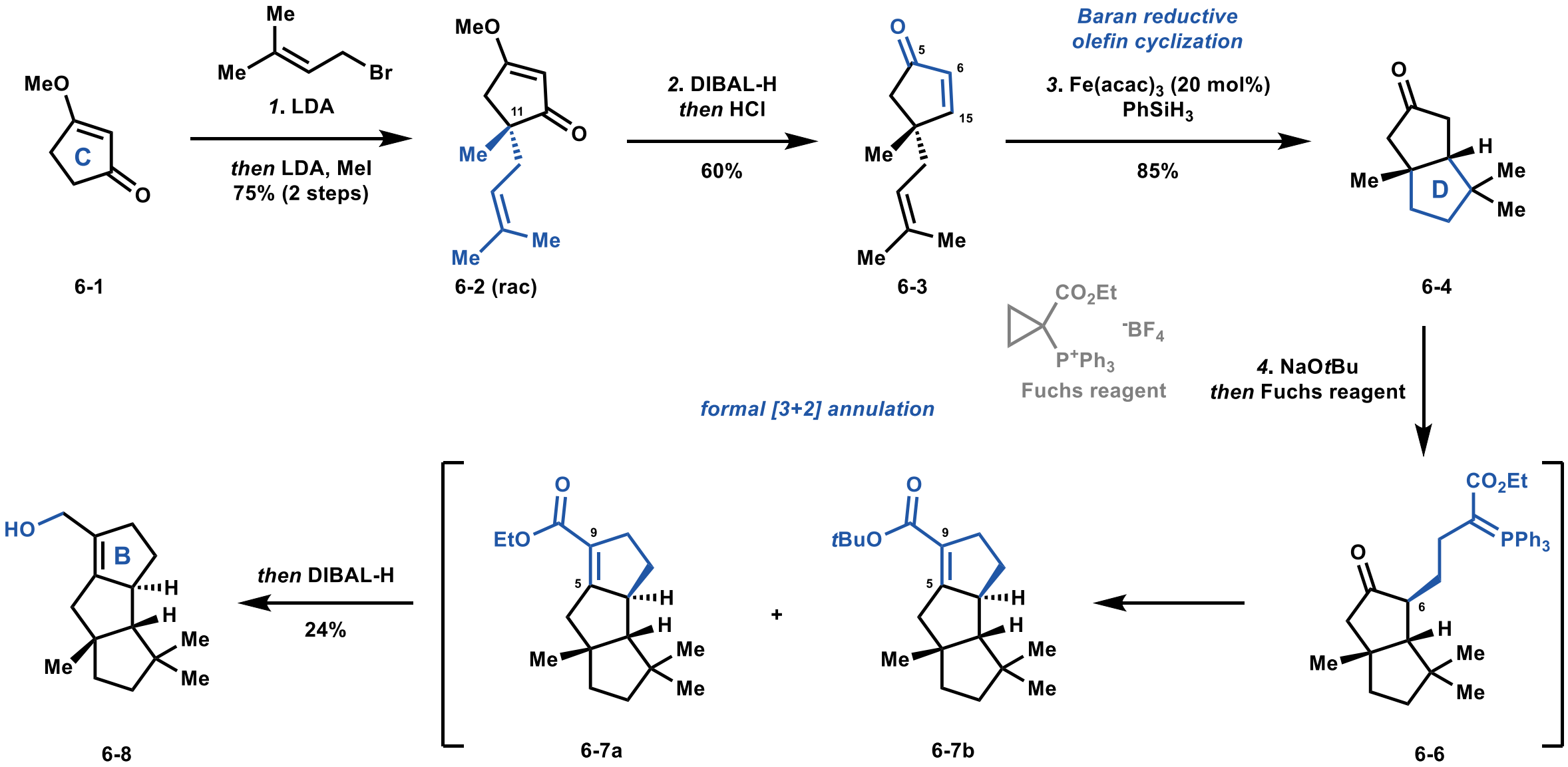
Total Synthesis of (±)-Conidiogenone B — *Dai* (2026)

Retrosynthetic Analysis



Bernard, J.; Zhang, Z.; Dai, M. *J. Am. Chem. Soc*. **2026**, *148*, 17190–17196.

Total Synthesis of (±)-Conidiogenone B — *Dai* (2026)



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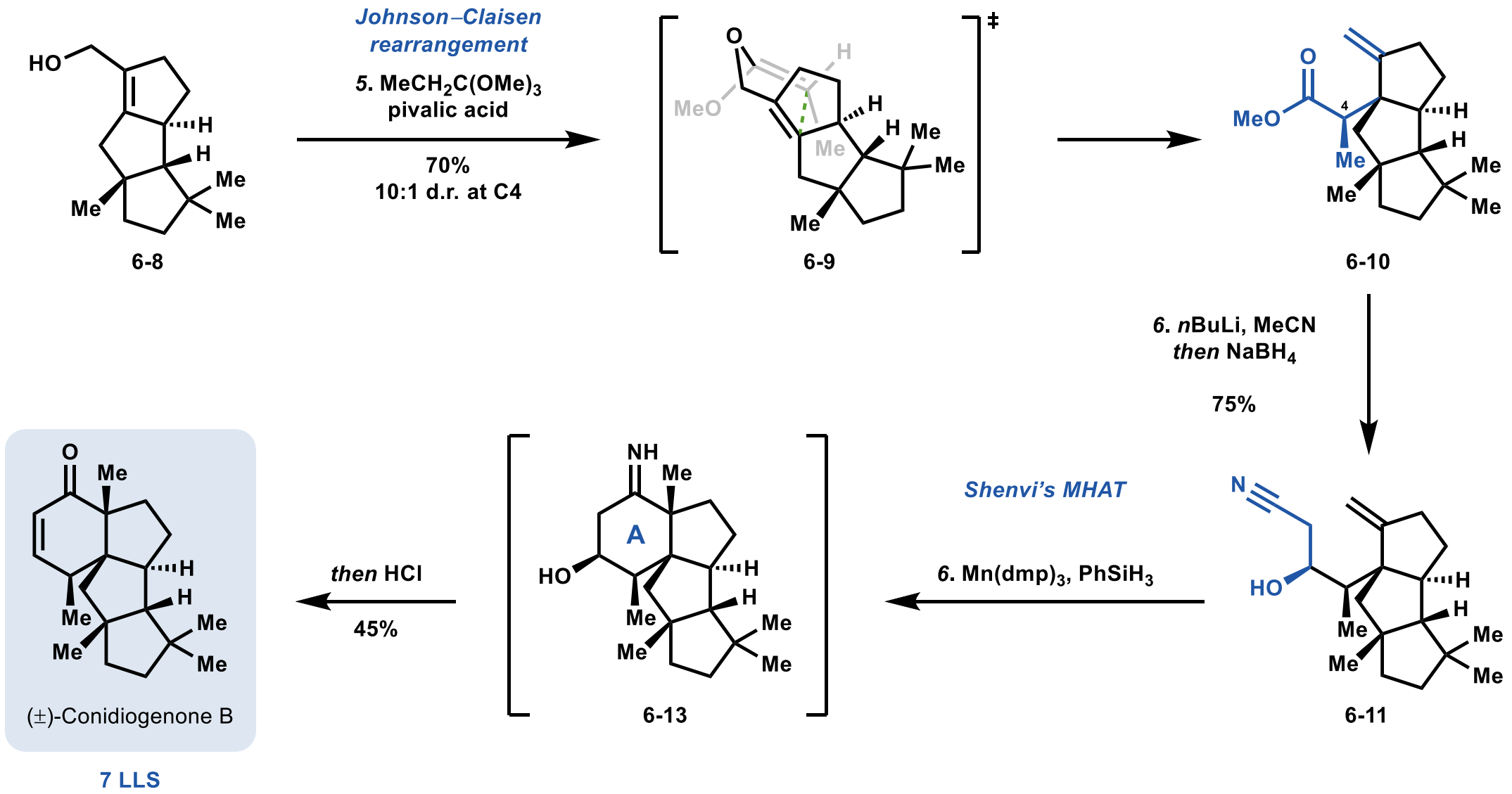
Total Synthesis of (±)-Conidiogenone B — *Dai* (2026)



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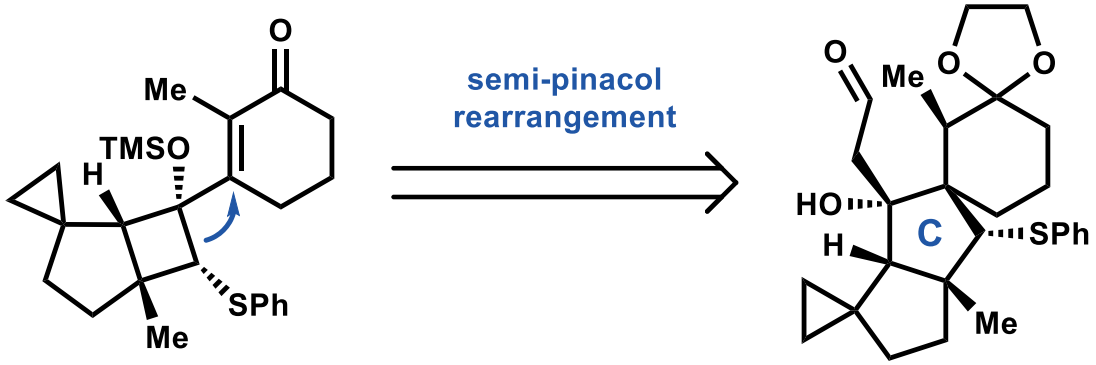
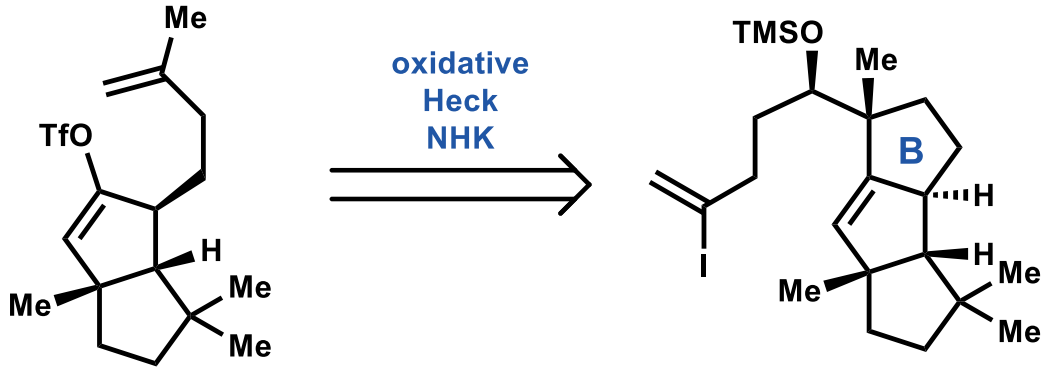
  - Scott A. Snyder (2019)
  - Hongbin Zhai (2020)
  - Sunkyu Han & Heeyoon Lee (2023)
  - Mingji Dai (2026)
- Summary

Summary

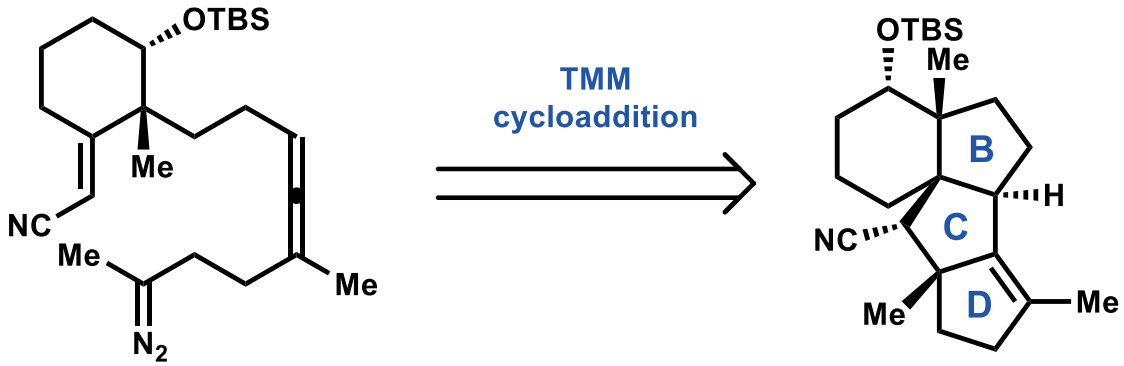
Tu (2016), 24 LLS
C: 7 steps
FGM: 17 steps



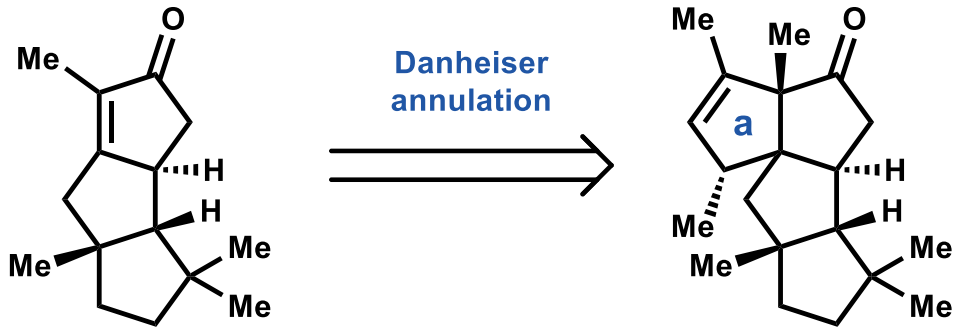
Snyder (2019), 13 LLS
C: 7 steps
FGM: 5 steps



Han & Lee (2023), 19 LLS
C: 7 steps
FGM: 12 steps

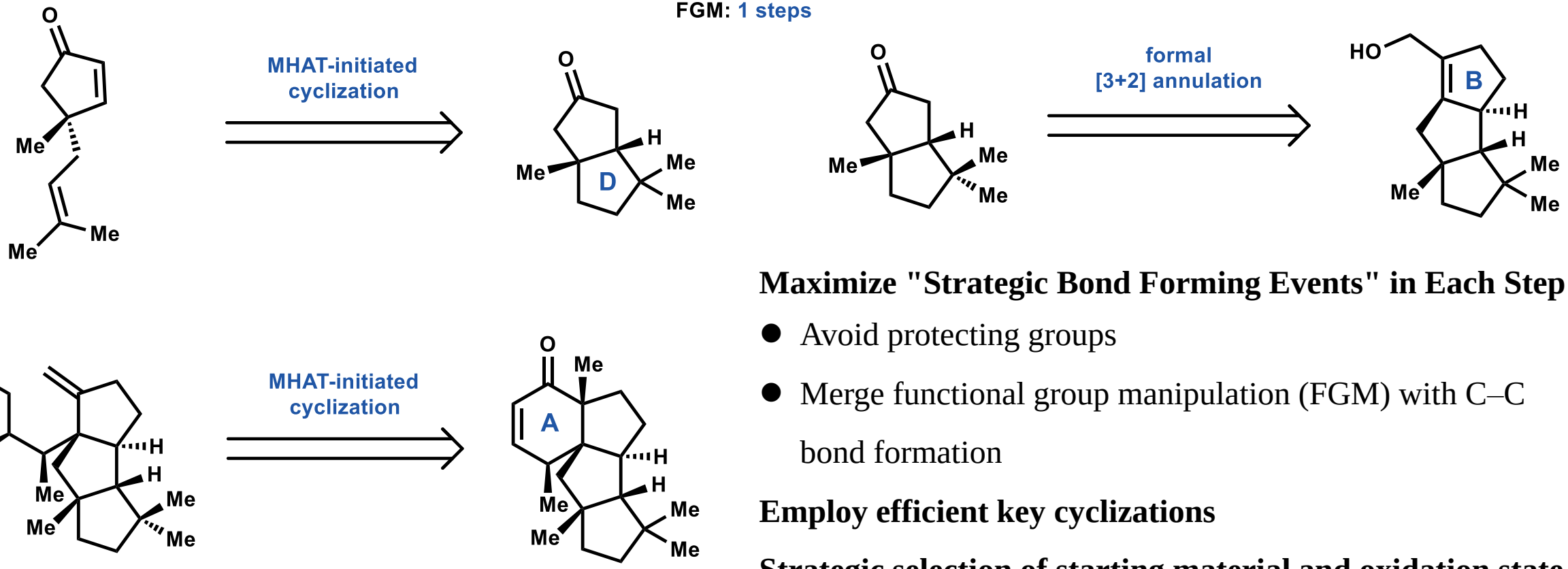


Zhai (2020), 15 LLS
C: 8 steps
FGM: 7 steps



Summary

Dai (2026), 7 LLS
C: 6 steps
FGM: 1 steps



Maximize "Strategic Bond Forming Events" in Each Step

- Avoid protecting groups
- Merge functional group manipulation (FGM) with C–C bond formation

Employ efficient key cyclizations

Strategic selection of starting material and oxidation state

Thanks for your kind attention