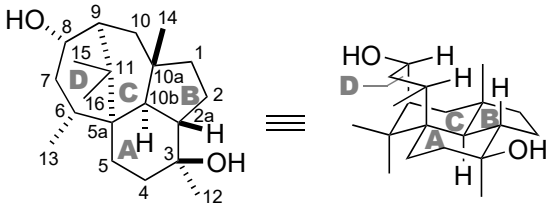
Problem Session (10) - Answer -

2024.8.31 Haruka Fujino

Topic: Synthetic Plan of (+)-Wickerol B Proposed by Inoue Lab Members

1. Introduction

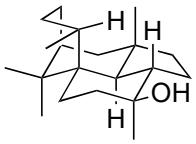
1.1 wickerols and related natural products



(+)-wickerol B
(a.k.a. trichodermanin A)

- **isolation**
  from a fungus (*Trichoderma atroviride* FKI-3849)
  Qin, L.-P. *et al. J. Nat. Med.* **2011**, *65*, 381.
  Ōmura, S.; Shiomi, S. *et al. Tetrahedron* **2012**, *68*, 9267.

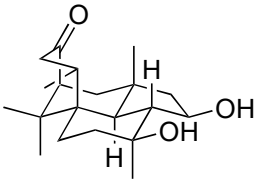
- **bioactivity**
  anti-influenza virus acitvity
  IC_{50} [μg/mL] against A/PR/8/34 strains: 0.07 (wickerol A) and 5.0 (wickerol B)



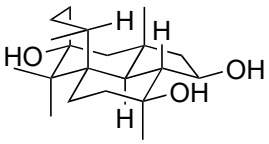
(+)-wickerol A

- **structural features**
  a unique 6/5/6/6-taracyclic core (The boat conforamtion of D-ring)
  1,3-diaxial interactions between the bridging ring (C6 and C8) and the axial C14-methyl group
  three quarternary carbons (two of which are stereogenic)
  trans-hydrindane ring junctions

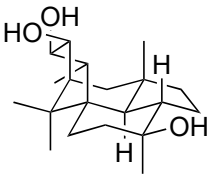
- **related natural products**
  trichodermanins C, D, and E
  (modest cytotoxicity)
  Yamada, T. *et al. Mar. Drugs* **2017**, *15*, 169.
  Yamada, T. *et al. Mar. Drugs* **2019**, *17*, 480.



trichodermanin C



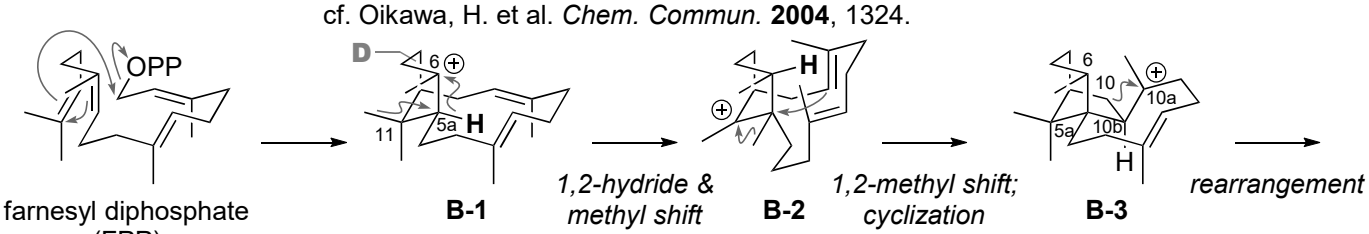
trichodermanin D



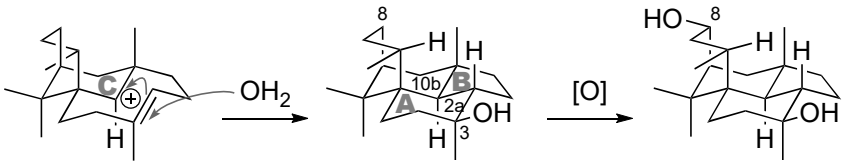
trichodermanin E

1.2 proposed biogeensis of wickerols

cf. Oikawa, H. et al. *Chem. Commun.* **2004**, 1324.



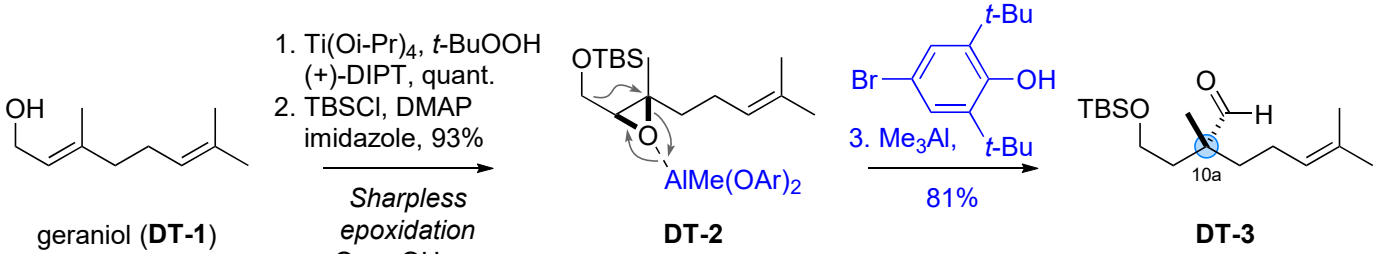
farnesyl diphosphate (FPP) → **B-1** → *1,2-hydride & methyl shift* → **B-2** → *1,2-methyl shift; cyclization* → **B-3** → *rearrangement*



B-4 → (OH_2) → **(+)-wickerol A** → ([O]) → **(+)-wickerol B**

2. Past Total Syntheses of Wickerols A and B

Trauner Group (2017) Liu, S.-A.; Trauner, D. *J. Am. Chem. Soc.* **2017**, *139*, 9491.



geraniol (**DT-1**)

1. $Ti(Oi\text{-}Pr)_4$, *t*-BuOOH
   (+)-DIPT, quant.
2. TBSCl, DMAP
   imidazole, 93%

Sharpless epoxidation

(+)-DIPT

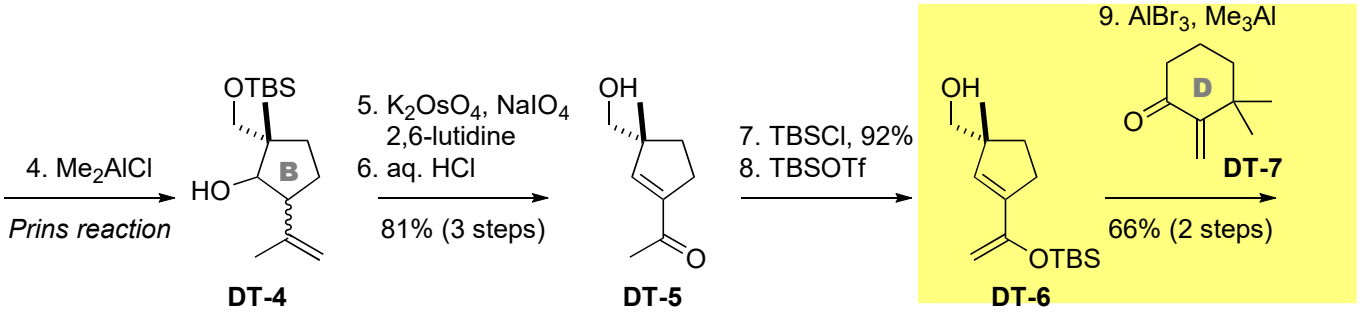
DT-2

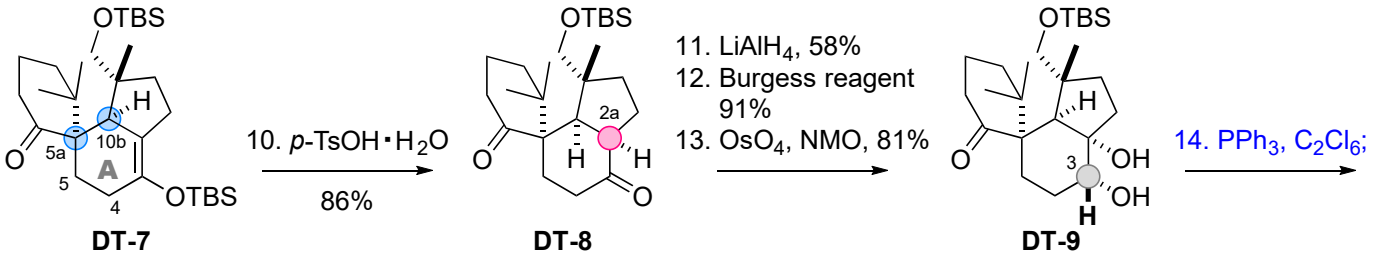
3. Me_3Al,

81%

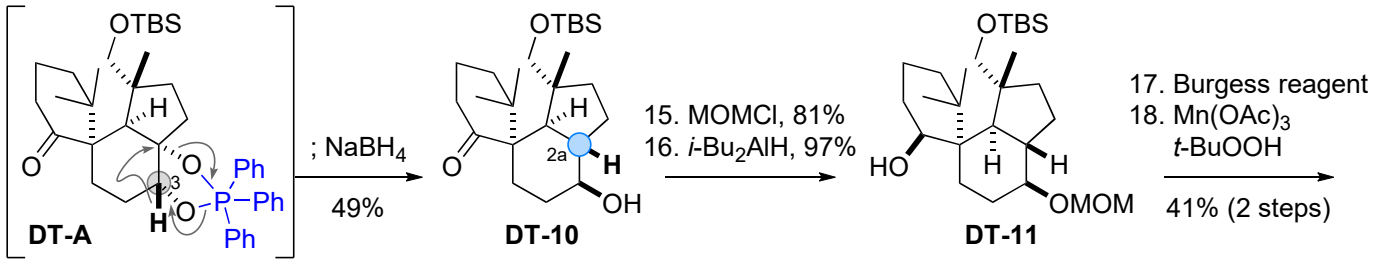
DT-3

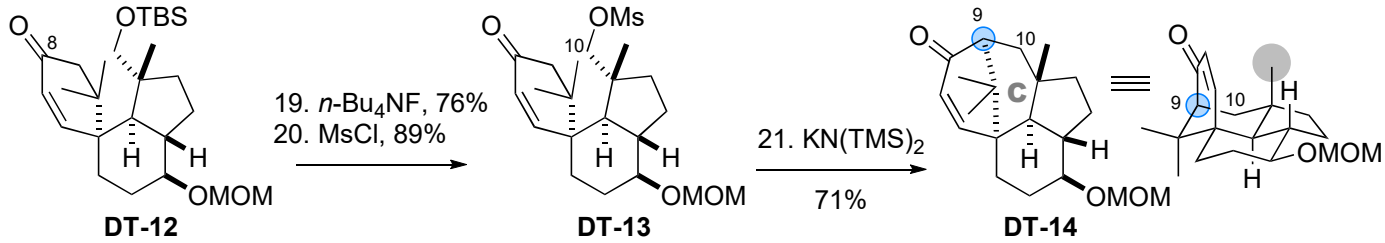
Yamamoto, H. *et al. Tetrahedron* **1991**, *47*, 6983.

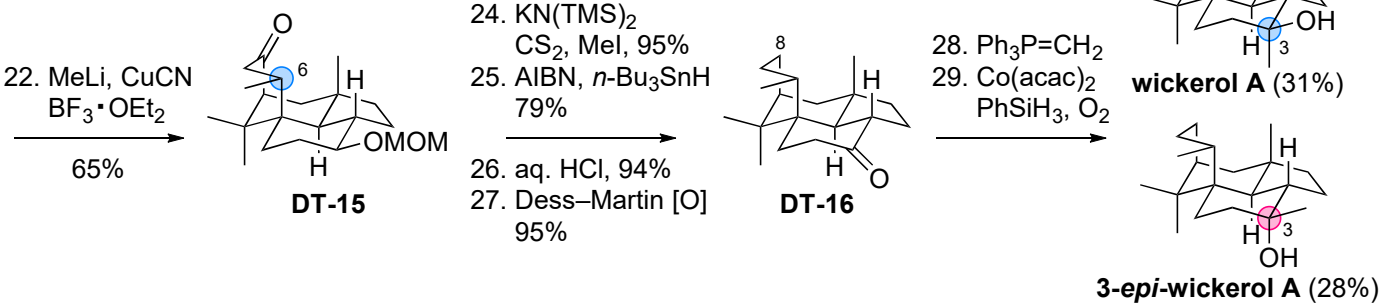




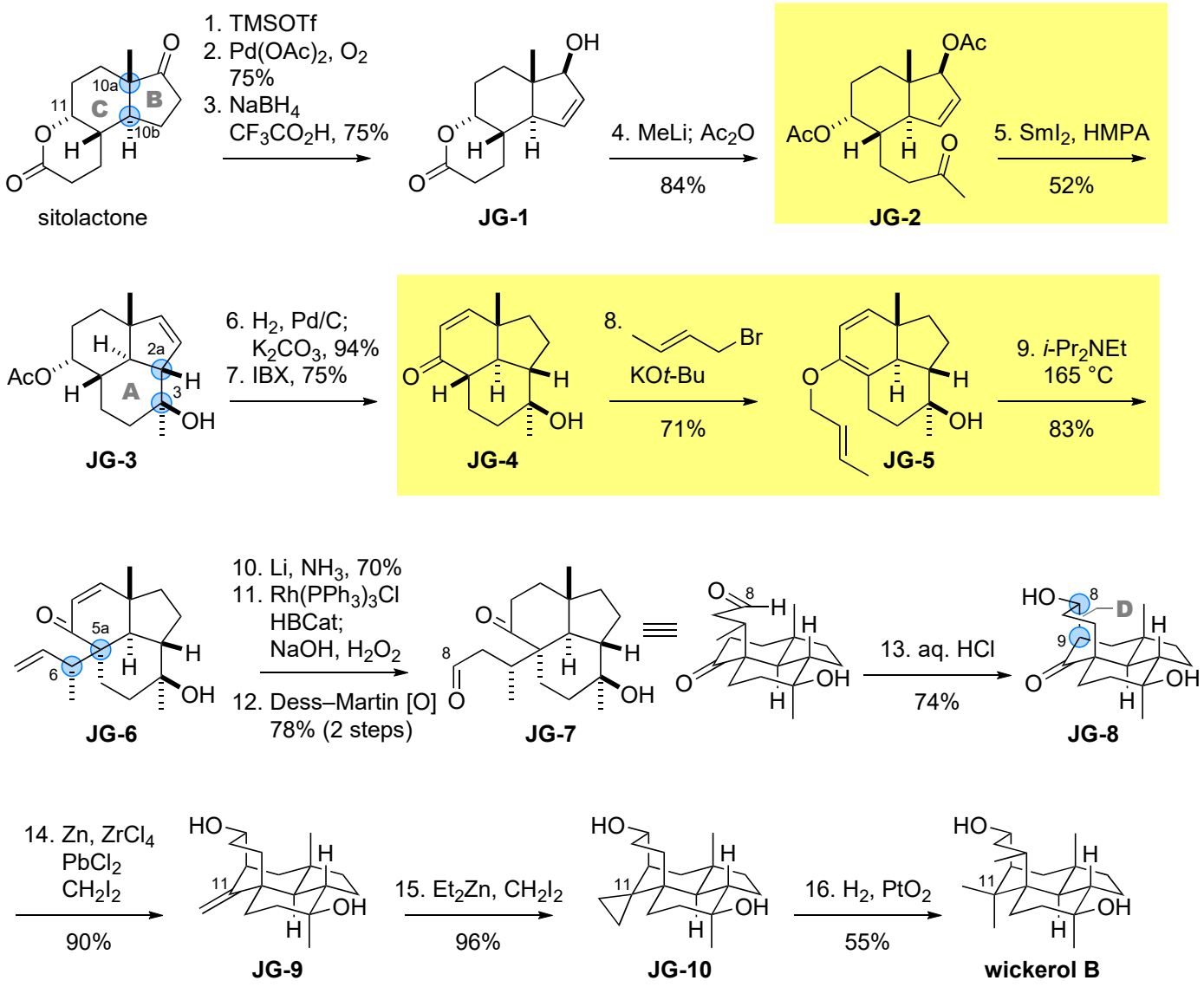
Grainger, R. S. et al. *Org. Biomol. Chem.* **2012**, *10*, 4926.





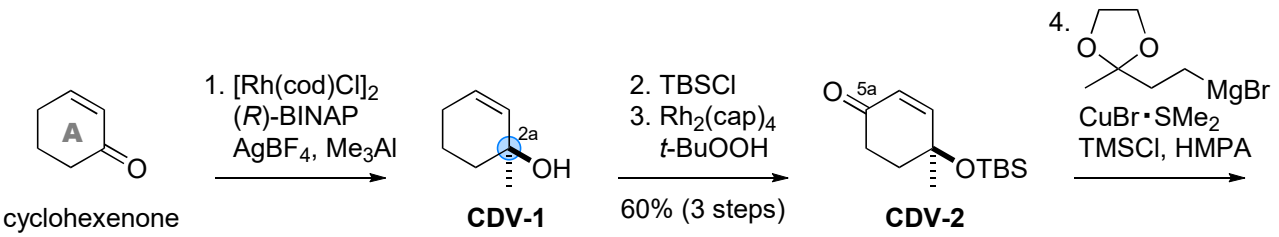


Gui Group (2020) Deng, J.; Ning, Y.; Tian, H.; Gui, J. *J. Am. Chem. Soc.* **2020**, *142*, 4690.

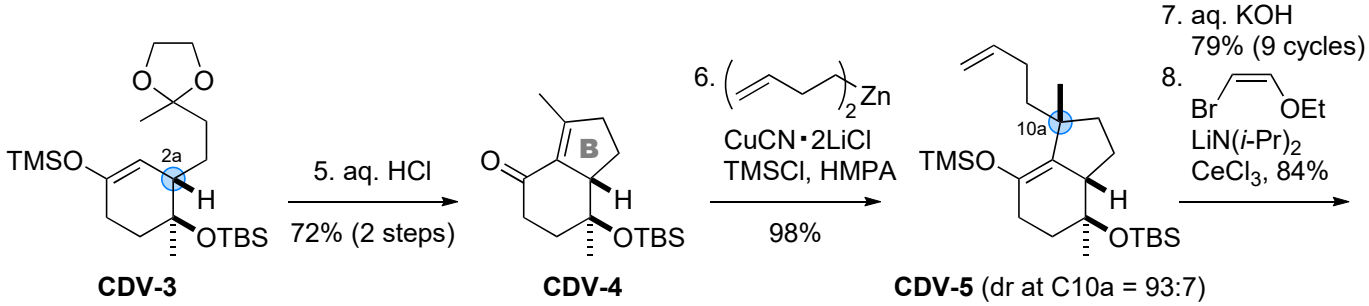


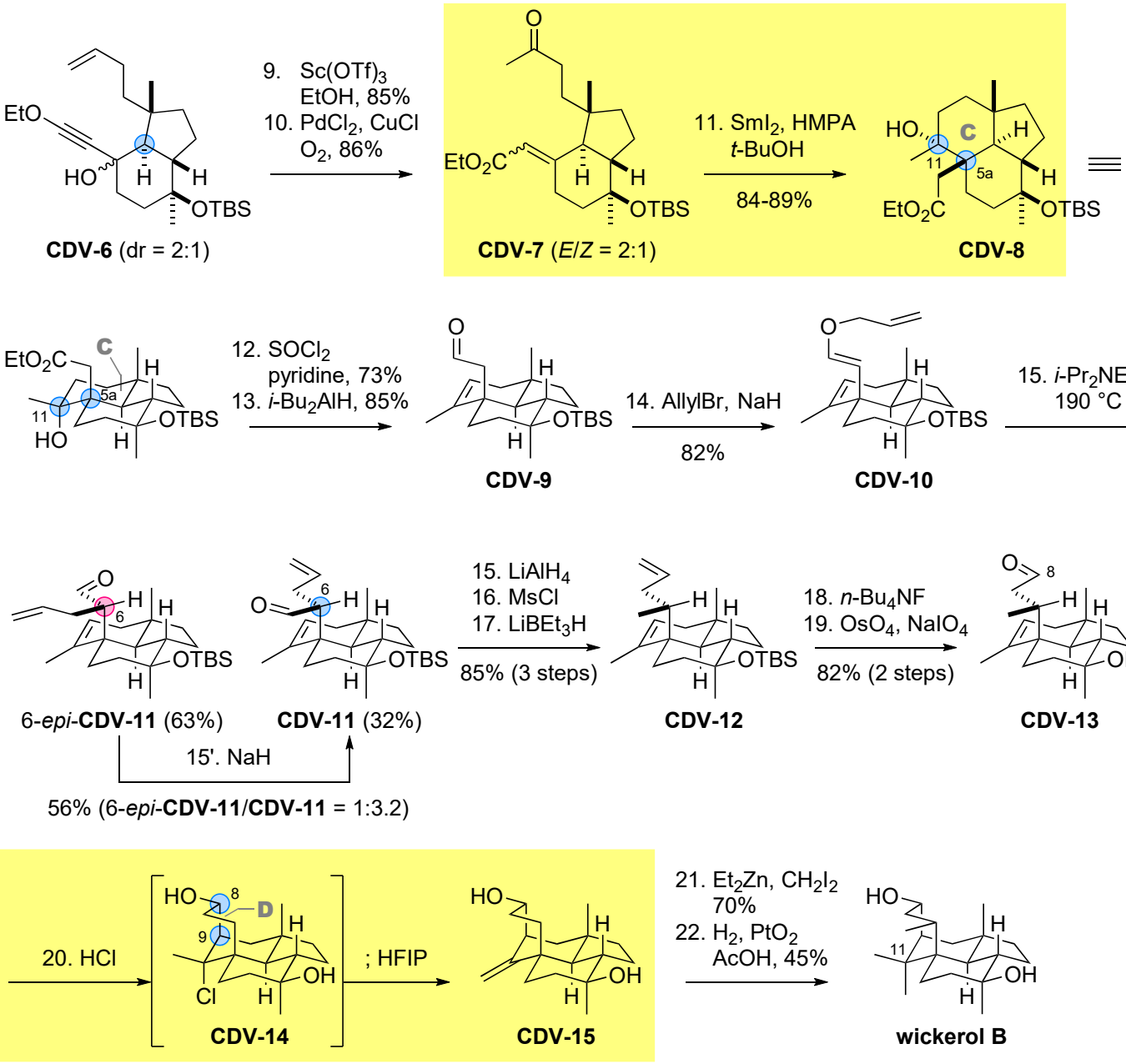
Vanderwal Group (2023)

Chung, J.; Capani Jr., J. S.; Göhl, M.; Roosen, P. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2023**, *145*, 6486.



von Zezschwitz, P. et al. *Chem. Eur. J.* **2013**, *19*, 16366.





Our original synthetic plans are closed to the public.